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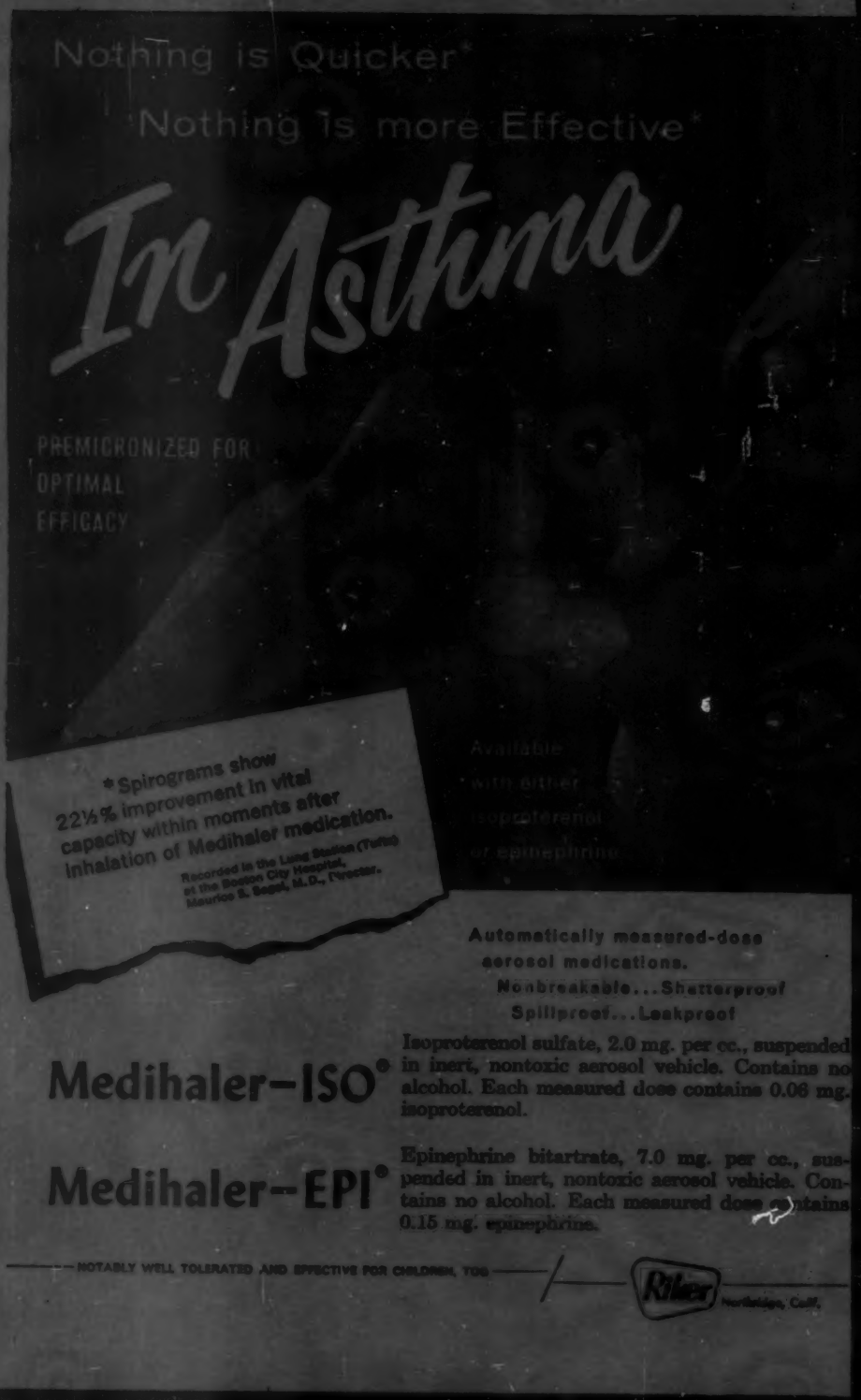
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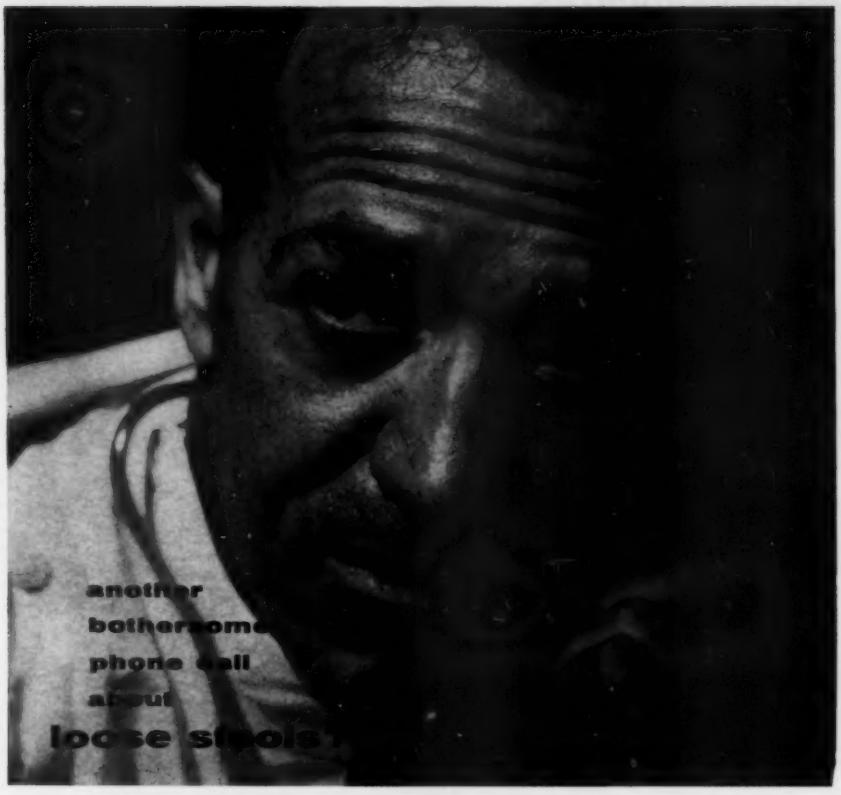

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1 mo.	36	0
2 mo.	27	1
3 mo.	12	1
4 mo.	10	1
5 mo.	14	0
6 mo.	8	0
7 mo.	19	0
8 mo.	11	0
9 mo.	10	0
10 mo.	8	0
11 mo.	11	0
12 mo.	10	0
	190	3 (1.6%)

†Exclusive of infants admitted with infectious diarrhea.

1. Frost, L. W., and Jackson, R.L.: J. Pediat. 39: 585-592 (Nov.) 1951.
2. Henrickson, W. E.: GP 8:51-56 (Oct.) 1953.

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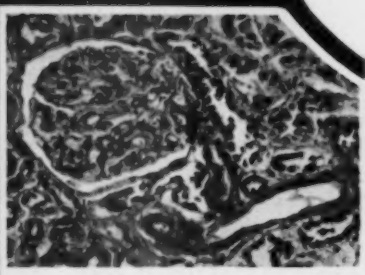

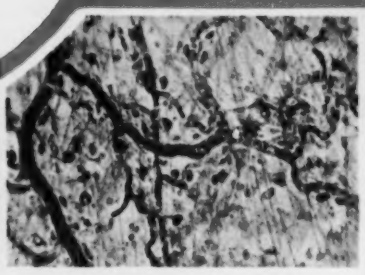

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*Lennox-Gibbs, F. A.: Epilepsy and Personality, in Arieti, S., ed.: American Handbook of Psychiatry, New York, Basic Books, Inc., 1959, vol. 1, p. 1054.

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CONTENTS

Youthful Offenses in Modern Culture 341
Harry L. Shapiro

Early Treatment of Ruptured Intracranial Aneurysms of the Circle of Willis with Special Clip Technique 357
J. Lawrence Pool

Neurological and Radiological Manifestations Associated with Spondylosis of the Cervical and Lumbar Spine 370
Joseph A. Epstein and Bernard S. Epstein

The Rise of Synthetic Drugs in the American Pharmaceutical Industry 387
Maurice L. Tainter and G. M. A. Marcelli

AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

VOL. 35, NO. 6 JUNE 1959

YOUTHFUL OFFENSES IN MODERN CULTURE*

The Tenth A. Walter Suiter Lecture

HARRY L. SHAPIRO, PH. D.

Curator of Anthropology, American Museum of Natural History, New York, N. Y.

WHEN Dr. Kruse courageously invited me to deliver the A. Walter Suiter Lecture and, furthermore, to talk on the subject of youthful offenses in modern society, I warned him that I was neither an expert on offenses, youthful or otherwise, nor on modern society. He replied, nevertheless, by suggesting that I take this opportunity to deal with the subject from the perspective of an anthropologist—something, of course, that no self-respecting anthropologist could bear to refuse.

Now, as I recall that conversation, my admiration of Dr. Kruse increases substantially, and I suspect, moreover, he is a man of parts with a natural flair as an angler. He had sized up his fish, selected just the right bait, and here I am.

Although I must admit that the bait was alluring enough to overcome any diffidence I might have had, I have no further apologies to make. The subject to which I am addressing myself is a deeply disturbing one,

* Presented at the Stated Meeting of The New York Academy of Medicine, November 6, 1958, under the auspices of the Committee on Public Health of The New York Academy of Medicine.

symptomatic, I think, of serious trouble in our society; and if, as an anthropologist, I can bring even a little understanding to it, I shall feel I have not been unworthy of Dr. Kruse's judgment or of this distinguished lectureship.

Dr. Kruse's choice of this evening's topic is particularly appropriate since Dr. Suiter, whose benefaction to the Academy of Medicine made this lectureship possible, had an active interest in one aspect of this subject. And I imagine that despite the success with which he overcame obstacles in his own adolescence, its rigor would have made him sympathetic to adolescents in our society who have been less successful and have succumbed to delinquency.

Youthful offenses, or in the current terminology, juvenile delinquency, is nothing new. Like a great many other consequences of community living, it has been with us for a long time, and as a phenomenon it is widely dispersed. For these reasons it is possible to see in it the multiple perspectives of time, space, and culture.

However, what seems ominous to many of us is the apparent increase in the frequency of such offenses against society, the violence associated with them, and the latent fear that the consequences may become out of hand and thus threaten our own safety and security. One has the distinct impression, from the kinds of remedies various people are suggesting, that these fears have overwhelmed good sense, or that the dimensions and the nature of the problem are totally misconceived.

I propose to make a distinction here between juvenile delinquency and individual criminal acts by youths. The former has become commonly associated with a distinctive type of adolescent and, I believe, arises primarily out of social maladjustments. It is behavior characteristic of adolescents acting in association with others. Or to put it another way, it is behavior that emerges from the interaction of a group of adolescents. An adolescent who has joined a gang because of neighborhood pressure, or for other social reasons, and who commits offenses in concert with other members of the gang, or even alone but according to the traditions of gang behavior, or even one who is committing antisocial acts because of various kinds of social influence, is in my definition a juvenile delinquent. His behavior may be reprehensible to society at large, but he is acting according to a definite and established pattern, acceptable and even obligatory for his gang or for his contemporaries who set the values and standards of his world. This is quite different

from the behavior of an adolescent who, overwhelmed by personal passion, frustration or rebellion, commits a criminal act. The offense may be the same, but the motivation and the cause are different. In the one case there is a social mechanism that channels the behavior; in the other, the action is personal and not primarily social. Now, obviously, such a distinction may break down in many instances, but it has a reality that explains some of the fluctuations in the frequency of juvenile delinquency and offers some hope that such behavior may be controlled by social measures since it springs from social causes.

I do not now propose to attempt either to demonstrate with the latest statistics an alarming rise in the curve of delinquency, or on the contrary, to minimize this pattern of behavior by a judicious analysis of the weakness of official figures. Whether juvenile delinquency is increasing, stationary, or even decreasing, it does exist to a degree that cannot be ignored and by virtue of its violence, its danger to human life, its disruption of security and its effects on the offenders themselves, has become a serious matter demanding our best efforts to understand and correct, or at least regulate.

Before proceeding further, however, I want to make clear my conviction that juvenile delinquency is a complex phenomenon arising out of a variety of causes. The overt behavior pattern itself may have a misleading aspect of uniformity, but like another kind of headache, it masks a number of different ailments. Single cure-alls are as likely to be effective in the one case as in the other.

Since juvenile delinquency falls into a kind of social pattern of its own, it is pertinent to ask, perhaps naively, what is society and why are offenses against it reprehensible? Society, of course, is a community of people who live within a common, organized system of institutions and/or customs. The members of such a community share, accept, and anticipate certain standards of behavior from each other. Society may be other things as well, but at its minimum it is at least this much. Now such a group, little or large, simple or complex, can function only if a sufficient number of its people abide by its laws or traditions. If everyone operated independently, or contrary to basic expectations, the society would collapse into chaos. The subordination, on the contrary, to law or tradition must be essentially voluntary or automatic. If submission to or acceptance of the law can be maintained only by naked force, then such a society is in dire and constant danger of revolution,

turmoil, and lack of security. Some element of force, of course, becomes necessary as societies grow large and complex. In small or primitive groups, exposure to the close observation of one's relatives and neighbors, and the power of their judgment on one's behavior, exact a high degree of conformity and punish a disregard for the accepted rights of others. Police or physical force, therefore, plays a minimal role in small, well integrated communities. But in the cosmopolitan, urbanized centers of large modern nations, recognition diminishes in proportion as population increases, and the individual acquires an anonymity that carries a certain freedom from group pressure and observation. Conversely, the enormous number of individuals and their constantly shifting relationship in large urban centers tend to discourage the kind of identification with and interest in the group that exists in small communities. Thus the indifference to others, the anonymity of the individual in the mass, weakens the effect of group opinion which is so powerful a force in small communities. Therefore authority and force, in the form of a policing system, become a necessary adjunct to large societies as a substitute for group pressure and to control the small minority that fails to conform to the law.

This does not mean, of course, that the great majority requires the presence of such a force to keep it within accepted boundaries of behavior—no police would be numerous enough to do such a job. Most people are by their training submissive to the requirements of their society. For one of the primary functions of any organized community is to train the young to the standards of behavior expected of them according to their role and place in it. The process of social conditioning begins almost from birth. At first the child is exposed to controls exerted by the mother and by the family. Rewards and punishments of varying kind and degree are meted out by parents, siblings, and other members of the family, according to the inherited patterns of the culture to which the family belongs. As the child grows up, he or she is exposed to the disciplines of still wider circles of individuals and institutions. In our society, for example, the school becomes an important surrogate as the child emerges from the dominance of the family. But in many other ways, intricate and subtle, the pressure of the larger society continues to mold and reinforce values, attitudes, and behavior. The literature we read, advertisements, television, radio, theaters, movies, the heroes and heroines evolved by our culture, and other multifarious influences affect

the child, the adolescent, and the adult.

Out of all this come individuals who conform subconsciously and without effort to the patterns of behavior developed by their society or culture. The toddler who, enchanted with some other child's toy, cannot understand why he can't simply walk off with it, learns—sometimes painfully—to respect the property rights of others. Properly trained by parents, conditioned by his peers, and educated by society, the former toddler now grown to man's estate has learned to curb or suppress socially forbidden behavior, and wouldn't seriously think of abandoning his beat-up car for his neighbor's shiny, new Cadillac.

Social behavior, therefore, is essentially a kind of automatic conformity to the standards and values of the community. We know almost instinctively what to do in the normal circumstances of group living, and equally important, we know what to expect of others. Social behavior takes on predictability. This obviously makes life easier to conduct, for we are not then obliged to spend a vast amount of time making decisions for the routine and repetitive aspects of our lives.

Because most of us are thoroughly conditioned to behave in conformity with such basic social requirements, we can by the same token expose ourselves to a certain risk of not being injured by others. If we could not, life would become either extremely difficult or even intolerable. Thus people who do not conform to these social expectations commit social offenses. How these are rated, depends on the society.

In some primitive groups, the mere stepping into a sacred taboo area might arouse the very highest degree of social outrage and incite the community to kill the offender; whereas murder committed in the same community might be condoned or relegated to the status of a family adjustment. From our point of view, this may appear irrational, but only because we, under ordinary conditions, value human life so highly. This relativity of social values has encouraged some writers to suggest that crime and social offenses are, after all, arbitrary, varying from society to society. This, I think, misconstrues the nature of social offenses. It does not matter if one society punishes what another condones. If the values of a society are abused, the function of that society is threatened and such abuses are legitimately offenses against it. In highly complex societies—in civilizations—the offenses are legally defined and evaluated in their seriousness, but the general principles are the same for all communities.

Obviously, in a well ordered, traditional society, the conditioning for social behavior works well and offenses when they occur are minimal. Why, then, do outbreaks of juvenile delinquency occur at all? Why do they sometimes show alarming increases in virulence, and why are the young frequently prone to commit such acts as we seem to be observing in our own society at the present time?

There have been times in Western civilization when economic conditions have borne so heavily on the economically depressed classes that mere survival was at stake. Certainly in pre-revolutionary Paris, and in the London of the early nineteenth century, economic factors must have played a not inconsiderable part in the delinquency, juvenile as well as adult, that flourished in those eras. The wonder is that, considering how badly the poor fared then and in other periods of European history, the rate of juvenile delinquency was not greater than it was. It is a measure of how strong social conditioning must be if it can restrain a hungry and depressed section of the population, for although poverty and economic oppression have existed for long periods of time in European history, violent revolutions are, after all, relatively rare. Indeed, when one looks at other areas where poverty has also been extreme, for example in India, in pre-Communist China, and even in Puerto Rico a generation ago, the juvenile delinquency is not commensurate with what one would expect if economics were the primary factor. For these reasons I do not consider economic factors alone as a very important element in our current frequency of delinquent behavior. Among the two most recent populations to settle in New York City, southern Negroes and Puerto Ricans, the economic conditions here, poor as they may be, are better than they were in the South or in Puerto Rico. The increase in delinquency in these groups has apparently taken place after their settlement in this urban area.

There are two aspects to youthful offenses: there is the offense, a species of social behavior or misbehavior; and there is the offender. Although they are inseparable, it might be useful to look at them as two separate sides of the same coin—social dynamics and the individual.

From my prefatory generalizations about society, it is obvious that if the agencies through which society conditions the young and determines their behavior are defective, or are working at cross purposes with traditional standards, the process of training and indoctrination will, to that extent, be deficient. This can come about in a variety of

ways, too numerous and intricate to analyze here. In general, large complex societies, compared with small homogeneous communities, always have a tendency to develop sub-cultures and other, even more marked, forms of social and cultural heterogeneity. This in itself need not be undesirable. But when social and cultural heterogeneity encourages conflicting tendencies within the society, the results can become significant in terms of juvenile delinquency.

Let me explain this point in a little more detail. There are, it seems to me in this connection, two forces that to some extent integrate and intensify a certain type of disharmony in modern society. One is the trend toward urbanization, and the other is the rate of technological change. Even in fairly homogeneous nations, the city generally occupies a peculiar cultural position. It is a place where traditional bonds between social classes are loosened, where distance between groups widens, and where older patterns tend to break down. Here all the divergent elements of a nation assemble and create a highly complex interplay of conflicting currents. It is no accident that revolutions are apt to occur in urban centers where the disparate and disaffected elements of a society are apt to meet, and history itself demonstrates how important the city is in the initiation of new ideas, new processes, and in the progress of civilization itself.

In modern societies, and nowhere more than in the United States, these characteristics of urbanization are no longer restricted to the cities, but have spread nationwide. As a result, the distinction between the city slicker and the country bumpkin is rapidly disappearing.

All this has happened in our time because in the last century the pace of technological change has gradually accelerated to an unprecedented degree. In the past, the social effects of technological progress spread slowly and could be more easily absorbed by society as a whole. Nowadays our technological revolution not only contributes to the stresses of urban life, but carries them with great rapidity throughout the nation.

If we think primitive man has been hard pressed by the rapid changes forced upon him by contact with Western civilization, our plight, although a self-induced one, is equally profound. We have only to think of the frequently cited effect of the automobile to realize how fast our culture and our way of life have been changed by its introduction. Within a little over a generation, the car has remodeled profoundly

almost every aspect of living, and has created problems that we have not yet learnt to solve. If we multiply the effect of this single technological change by the host of changes that have beset us—the cultural influence of radio, television, movies as examples—it is no wonder that it often seems that one generation has difficulty understanding the next. For the effect of all these introductions into our lives is not the same on our children as it is on those who were nurtured in a different environment. Influences that simply do not penetrate our cultural skins, or if they do are rejected, exert a profound influence on our children. The inevitable result, when changes of this kind come thick and fast, is to develop an increased cultural separation between generations and, consequently, a fruitful source of conflict between them. In normal, primitive societies, or in our own more isolated communities, comparable cultural separation between generations did not exist.

The significance of this for some aspects of juvenile delinquency lies in the fact that the family, which was the traditional center in our society for adolescent activity, has lost much of its authority. Adolescents who in an earlier day expected and were expected to participate in family affairs, to use their homes as the scene of their social activities, and who were anyway unable to get very far away, do so less in these days. The young man in the family car, or in his own jalopy, prefers to take his "date" as far from home as possible. Various commercial establishments for his entertainment are now easily accessible to him. His contemporaries set standards of behavior which his family have little chance of discouraging. The upshot of all this is an increasing separation of adolescent from family influences, a lack of the sympathy and understanding that, shared in common by parents and offspring, can serve to preserve the values that govern behavior.

The kind of conflict that grows out of such conditions can be seen perhaps more clearly in parallel situations among primitive people than they can in complicated modern societies. One of the tragedies that has with increasing frequency overtaken hundreds on hundreds of primitive cultures in our own time is this, perhaps inevitable, weakening of the traditional patterns by new and often revolutionary influences. The introduction of Western civilization to many primitive groups is by the very nature of the contact rapid and overwhelming. It has meant a loss of prestige for the ancient codes and values and the development of conflict between the old and the new, resulting frequently in behavior

that is strikingly like what we call juvenile delinquency. Such dislocations hit the adolescent in particular. He has not been hardened in the mold of his inherited tradition as his elders have been, and his often inadequately based interpretation of the new does violence to the community's patterns. Although such advocates of the new ideas may eventually convert the community to a new synthesis, the transition is often a period of stress and strain. Many groups have tragically foundered in the passage.

But conflict within modern society, arising out of the rapidity of change and the consequent difficulty of social values to keep pace with it or to adjust such changes to traditional values, is further complicated, particularly in the United States, by several other factors.

From its very beginnings, the United States has been characterized by social mobility. The various groups that have successively immigrated here have each found themselves liberated from the rigid bonds that kept them within inherited social classes. Although most of the immigrant groups entered the hierarchy of our society at or near the bottom, they found in it more abundant opportunities for advancement, a more fluid social organization, and generally speaking, fewer barriers to a rise in the economic, and consequently the social scale, than they would have in the old countries. Indeed, we as a people have always been proud of this. We speak of our country as the "land of opportunity"; we affirm that any American child can aspire to be president. It is a cherished value that most of us would not have otherwise. But it can and does create a highly competitive situation—healthy and perhaps desirable under certain conditions. When, however, symbols of status replace reality and become a measure of success, where success is all important, their possession becomes essential. Now most societies are highly sensitive to status symbols, but ours in addition affirms that everyone should want them, that those who do not are lacking in American spirit and drive and are failures. Keeping up with the Joneses permeates all our communities. Adolescents, who normally want to be as like their fellows as possible and have what they have, are particularly susceptible to status symbols. The urge to achieve them is enormous. But if the deterrents are weak, if social conditioning is defective, the urge expresses itself in delinquency.

This urge is underlined by the mass media so typical of our times. The movies and other popular forms of entertainment set before the

youth of modern society a galaxy of heroes and heroines, a picture of luxury, of morals and of life that is depicted in the most alluring manner, frankly designed to appeal to the largest possible audience. The unreality of this world and its meretricious standards are not easily penetrated by youngsters of little experience. The ideals displayed are purely commercial and artificial.

Insofar as the domination of mass entertainment by the standards of crude commercialism has been permitted and accepted by the public, its products do arise from the culture. But they do not represent the best of it and may, in fact, be inimical to it. Their effects can scarcely be good. How bad they are, is difficult to assess. If the delight that many adolescents take in them (without exhibiting much evidence of discrimination) is any index, one would have to say pretty bad. I am far from claiming that the false values and the anti-social goals glorified by the movies, television, and comics lead directly to juvenile delinquency. But in a world where material things have an exaggerated value and where the young are encouraged to want them desperately, cinematic fantasies that seem to make it all desirable and easy to attain cannot fail to have some effect. Such influences can only contribute and reinforce tendencies either latent or budding. To see in all the glamor of a movie production varieties of socially disapproved behavior admired and rewarded, can certainly not be said to act as a deterrent.

History has added another element of tension and conflict to American society that is especially characteristic. Because the United States was settled by successive waves of migration, we have almost from the beginning been multi-national in origin and multi-racial. Each new migration wave brought to the society and culture developing here patterns of belief, custom and behavior that were different, sometimes repugnant to American standards. It would require a great deal of time to go into the interplay of forces that this experience (repeated over and over) released. The plain fact is that immigrants into this new cultural and social milieu were usually at a loss to understand fully the values and subtleties of their adopted country.

In the United States this situation, full of potential conflict, was aggravated by several circumstances. The immigrants were generally drawn from economically depressed classes, poorly educated and ill equipped to contend with the demands of the American scene. Often they spoke an incomprehensible language, practiced a strange religion,

and followed customs that struck Americans as odd or bizarre. The older inhabitants often distrusted and were deeply suspicious of the newcomers. But perhaps as significant as any single factor, many of the waves of immigrants were overwhelming in number, so that native Americans felt inundated and threatened. With lack of understanding on either side, the results were inevitable. The immigrants were either ignored as a necessary evil, rejected as inferior, or actively fought as a menace.

The immigrants, themselves, were more often than not insulated to a certain extent from these attitudes. Occupying the lowest economic levels, their contacts were limited and their demands on society at a minimum. Unfamiliar with American mores or the English language, they huddled together in special quarters where they could find comfort and support from their cogeners. Anyway, they were grateful for whatever improvement migration to the United States had brought to their lot. Even the wretched conditions, by native American standards, in which they lived were sometimes better than they had known. In effect, the immigrant groups, by virtue of their numbers and their residence pattern, were able to establish themselves in a transplanted, if temporary, sub-culture of their own, recognizably different from the prevailing patterns in the United States.

Their children, the second generation, presented a totally different problem and one that in our urban centers has set the stage for much of what we call juvenile delinquency. Upon this generation, born in this country of parents born in another, fell the real burden of bridging the gap between the mores and culture of their parents and those of their native country. The immigrant parents had been formed by one society and equipped by it with guide posts serviceable enough even for this new world. The children, once they were exposed to the molding influences of the United States, were eager to become Americans, to speak English, and to abandon the old country ways. The normal respect for the authority of the parent suffered grievously in these circumstances, since the American-born children looked upon their parents with a curious mingling of unease and shame at their foreignness, irritation with their outmoded standards when they interfered with their own, and superiority over their ignorance. And without authority and respect, the transfer of traditional values from parent to child is difficult. The continuity of generations upon which society depends is broken or

loosed. And the parents, bewildered by the rebellion of their children, were often unable to cope with them since the new society in which they now lived did not offer the support they might have received in the old country. Thus the family, so vital a link in social conditioning, frequently was unable to exercise its function in these immigrant subcultures that were slowly and painfully adjusting themselves to a new milieu.

Children cut loose from the familial control were easy victims of the unhealthy influences of the street society that flourished, and too many became delinquents. It has been a recurrent fact that each immigrant group in our crowded urban areas has tended to display this typical expression of social maladjustment in a high frequency of juvenile delinquency.

The tendency has more often than not been aggravated by corroborative circumstances that I think are worth mentioning. One is the need that most of us feel to be a part of a group. Where the parental culture was repudiated, the second generation children sought to find a place in the society and culture of the United States. The astonishing thing is how many succeeded, but the casualties were also high. Since the family could not provide an acceptable social framework, many second generation adolescents identified themselves with the nearest substitute —the company of others in the same situation—and a kind of new culture and society evolved in the streets and neighborhoods. This was a spontaneous outgrowth, but one not disciplined by traditional controls. Often it was a harmless association that might be dropped like a cocoon as the adolescent made progress in his integration with the larger society. But frequently enough it led to anti-social and predatory behavior because the rewards and the prestige system of these groups demanded it. And once committed, many young people found it difficult to break away.

How much the growth of such groups or gangs arose out of rejection by the dominant culture is impossible to say. The impression one gets from various sociological studies, from conversation, and from the literary genre that deals with minority groups, strongly reinforces the conviction that it is not a negligible factor. If the path of integration with the larger social group is blocked and the aspirant is thrown back, he may all the more readily affiliate himself with these marginal units.

I have already mentioned that juvenile delinquency is often high

in second generation groups in our crowded urban areas. But the phenomenon is not confined to this country, although, because of our population history, it is especially notable here. In European cities where immigration has settled similarly foreign and alien masses, the same tendency toward delinquency arises and for the same reasons.

That gang society is culturally orientated is particularly evident in the way these marginal adolescents organize themselves. They emblazon their jackets with insignia that show the world they belong. They wear clothing that is almost a kind of uniform. They form tightly knit groups with intense loyalty to the group and to one another, and on the other hand, hostility for any outside group. Courage or daring is admired and used as a mechanism for establishing status and prestige. Initiation, sometimes with elaborate ritual, may mark entry into the group.

All these characteristics are typical of primitive, cultural organizations. And it is more than interesting that they should become associated with gang life in our modern cities. Adolescents, not finding satisfying social mechanisms in their own environment, create them. The deep need to belong, to have a place, and to express oneself socially cannot be denied. One is almost tempted to say that some reaction of this kind is a good and hopeful sign. The long process of human adaptation to culture has endowed us all with a capacity and consequently a desire for association with our fellows. In many ways we cannot express ourselves fully, exercise deep-seated drives, and obtain certain types of satisfaction unless we do so through social mechanisms, formal or informal. The point I am making, therefore, is that the gang structure of adolescent society in certain areas of our cities is, under the circumstances, a natural one. Its very existence reflects a strong capacity for socialization that cannot be discouraged. The unfortunate thing is its development outside the restraints of the traditional structure of society. The spontaneous emergence of gangs to fill social voids at least implies that, directed by useful social channels, this drive could be salvaged and prove valuable.

A common confusion about gangs is the assumption that they are primarily organized to commit offenses. I think this is fundamentally wrong and as long as it exists will interfere with a realistic understanding, essential to dealing with the problem of juvenile delinquency. The adolescents who organize and join these groups do not, in most cases, do so deliberately in order to prey on society. The offenses against society are in a sense incidental. They are expressions of organizations

which, having sprung up to fill a gap that has developed in society, have not been domesticated or fitted into the traditional behavior patterns. Unregulated, and in a sense free-wheeling, these ephemeral groupings tend to develop individualistic behavior that can and does lead to offenses. It is important to recognize that such youthful group behavior is initially quite different from the behavior of adults committed to a life of crime. The key to the former is social fellowship. This does not, of course, mean that youthful gangs may not be fruitful sources of recruitment for the activities of the latter.

One of the impressive things in a so-called primitive society is the participation of every one in both community and family activities. The process begins at a very young age, and suitable tasks are assigned to children we would consider nowhere near ready for responsibility of any kind. Indeed, this is an important part of education and training for adult skills and future roles. I have seen fathers take their small sons on their expeditions and initiate them in the traditional knowledge of a breadwinner. And little girls, hardly more than babies, begin to learn household tasks and even take full charge of their younger sibs. Thus these children from an early age play a real and significant role in their family life. They have an established place in the society, they discharge obligations placed on them with astonishing reliability, and they have a dignity that comes from such responsibilities.

Modern society, Western society, the United States in particular, has relegated the child more and more to a peculiar non-participating membership in society. There are reasons for this. More and more of us live in apartments that don't belong to us, and for which we have no special responsibility except to pay the rent. Any repairs or chores our apartments require we expect to be attended to by paid mechanics or superintendents. We don't shovel the snow from the sidewalk, we don't fire the furnace or sift the ashes afterwards, even if these tasks were there to do in this age of automatic gas or oil burners. Even minor repairs seem too difficult when there is someone to do them for us and, anyway, why should we do these things for someone else's property? The chores that in an earlier age in this country were the allotted task of most boys no longer exist, and those who live in typical urban environments have virtually no responsibilities in the economy of the family.

Besides this freedom from a contributing role in the family, boys

nowadays are not permitted to take on full-time employment. The appalling abuses of child labor in the nineteenth century evoked a public revulsion that gradually brought about labor laws that were based on humanitarian principles and not on social ones. They had the effect of prohibiting all young people under the age of 16 from working. This, combined with compulsory school attendance, has served to delay our adolescents from the assumption of a place in our economy except as consumers.

Besides all this, education has become for most Americans a key with which to open the doors of advancement and success. Every responsible parent sets as high an educational goal as possible for his offspring, and will sacrifice a great deal to further such ambitions. The extraordinary increase in the enrollment of our upper schools is a testimony of this national premium on education. No one will, I think, seriously deny the values of education, although many might argue about the virtues of our particular system. But there is no denying that, for whatever causes, a not inconsiderable number of the juvenile members of our society are not making the best use, or even a good use, of the educational system that is provided. They go to school—they are physically present in the classroom, but the spirit is not there.

This is a dangerous observation to make, particularly in a democratic society which not only believes firmly in education, but even more, that every child is entitled to a college education. I am not challenging this belief, although I think it can be done. What I am saying is that an uncomfortably large number of boys and girls, in high schools particularly, are reluctant scholars, uninterested in their work and potential sources of trouble. This lack of interest may reflect bad preparation, poor pedagogical techniques, psychological difficulties, adolescent preoccupation with maturing physiological processes, social influences like those I have already described, or plain intellectual inability to deal with concepts of academic subjects. But whatever the cause, adolescents who are unwilling scholars, who refuse to do their work at school or at home, whose interest is neither captured nor in any way engaged by their studies, are at a loose end. Since they cannot work and have no domestic duties or chores, they are ripe for the life of the streets, gang associations, and other forms of diversion that easily fill the vacuum. Since young adolescents are normally high-spirited, full of energy and eager for adventure, the stage is set for behavior that can readily become anti-social.

It is a curious blindness on our part to fail to recognize that as we lengthen the period during which the young are segregated from social and economic responsibility and are treated as immature, their physical development is not equally delayed. In earlier days and in other places, youths of 16 to 17 were already carrying a man's load. It was no uncommon thing in our own immediate past for youths only little older to have already commanded ships and to have led men in dangerous enterprises. And in many primitive groups, even provision for the sex life of adolescents of comparable age is arranged in a socially acceptable manner. To our failure to face the fact that our adolescents, too, at this age are acquiring the strength of men, the desires of men, but not the restraints that come from discipline, responsibility, or socially satisfying activities, must be laid some of the blame for the conditions we vociferously deplore.

In this necessarily rapid survey of the phenomenon of juvenile delinquency, I have, I am all too aware, omitted to mention a number of factors that some observers have stressed in their commentaries. For example, the spread of drug addiction has been often cited as a significant determinant of crime. And I think the evidence can scarcely be denied that the need to obtain money to buy drugs has driven many adolescents to commit offenses. But from my point of view, this is a secondary cause arising from the kind of basic social maladjustments I have been describing.

Similarly, I would not deny that broken homes, psychiatric situations, and indeed a number of other possibilities also, might be cited. But these, too, seem to me to follow from a more fundamental social and cultural malaise. You may recall that I began with the conviction that juvenile delinquency is, in fact, a complex phenomenon.

The remedies consequently, in my opinion, must attack the basic social and cultural situation that forms the medium in which juvenile delinquency thrives like germs. To offer such palliatives as more playgrounds, desirable as they are, does not begin to touch the heart of the disease. It requires, to begin with, the kind of attention it has rarely received—sympathetic and objective investigation at a basic level. And, if my analysis has any validity, it will demand equally basic social measures that will not be easy to apply. Society will have to decide whether the effort is worth while.

EARLY TREATMENT OF RUPTURED INTRACRANIAL ANEURYSMS OF THE CIRCLE OF WILLIS WITH SPECIAL CLIP TECHNIQUE*

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AN intracranial aneurysm, like a live bomb within the head, can explode at any moment. Therefore surgical treatment should follow the diagnosis of aneurysm as soon as possible. The timing and type of surgical intervention will depend largely on the age and condition of the patient and the location and character of the aneurysm.

Most intracranial aneurysms are of the congenital saccular or berry type that arise from the circle of Willis, or more rarely from its peripheral branches or the vertebral-basilar arteries. There is a 13 per cent incidence of multiple aneurysms[1, 2]. The location of intracranial aneurysms is approximately as follows:

TABLE 1

Artery of Origin	*Incidence*
Internal carotid-posterior communicating	34%
Anterior cerebral-anterior communicating	25%
Middle cerebral	12%
Vertebral-basilar system	6%
Infraclinoid including arteriovenous type	3%

SYMPTOMS AND SIGNS

Clinical indications of an intracranial aneurysm are first apt to become apparent between the ages of 30 and 60 years. Subarachnoid hemorrhage, usually the first evidence of such an aneurysm, is mani-

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fested by sudden excruciating headache followed by nuchal rigidity and lethargy. Photophobia, striate retinal hemorrhages and coma may also develop. Lumbar puncture of course reveals a bloody cerebrospinal fluid that is usually under increased pressure. The following tabulation indicates the approximate incidence and causes of subarachnoid hemorrhage, and points up the need for bearing an aneurysm in mind whenever subarachnoid hemorrhage occurs.

TABLE II—SPONTANEOUS SUBARACHNOID HEMORRHAGE

Causes	*Incidence*
Intracranial aneurysm	50%
Arteriovenous malformations (angiomas)	20%
Unknown etiology	15%
Cerebral arteriosclerosis	8%
Brain tumor	7%

In close to one out of three cases of proven intracranial aneurysm, subarachnoid hemorrhage is not a presenting symptom and may never occur provided appropriate treatment is promptly instituted. In such cases, as also in many of those who have bled, the diagnosis and location of an aneurysm may be suggested clinically by focal symptoms such as intermittent unilateral headaches, often resembling migraine, or retro-orbital pain followed by ptosis, pupillary dilatation and oculomotor weakness which are so commonly associated with aneurysms of the internal carotid and posterior communicating arteries.

Contralateral seizures, hemiparesis, or reflex and sensory signs are more apt to be associated with an aneurysm of the middle cerebral artery, while visual field changes similar to those associated with pituitary tumors, and mental confusion, may be caused by an aneurysm of the anterior communicating artery. Aneurysms elsewhere, including those of the vertebral-basilar system, usually result in symptoms and signs clearly pointing to their location.

It is important to note that contralateral hemiplegia, abnormal sensory and reflex signs, or mental obtundity may also be due to regional or remote circulatory insufficiency of the brain caused by the cerebral vasospasm that so frequently develops within a few hours or days after

an intracranial aneurysm has ruptured[3, 4].

Progression of any of these signs, moreover, is a danger signal that may indicate hematoma formation, serious extension of cerebral vasospasm, or an enlargement of the aneurysm sac that threatens imminent rupture. Immediate surgical intervention is thus all the more urgent in order to prevent irreversible brain damage and death. Prompt surgery is of course also advisable, even when no such signs are apparent, in order to protect the patient from their occurrence.

Angiography

Definitive diagnosis by angiography is obviously essential whenever an intracranial aneurysm is suspected. Cerebral angiography by the carotid route is now relatively safe, thanks to newer contrast media like Hypaque[5], the risk of complications being less than 3 per cent. Angiography may therefore be done quite safely *at any time*, on any but the very ill patient, to establish the diagnosis, location and character of an aneurysm and any associated pathology such as a hematoma or edema of the brain. As an important additional guide to surgical management, *bilateral* angiography should be done (and vertebral visualization when indicated) to determine the presence of multiple aneurysms, serious anomalies of the circle of Willis, and the location and extent of cerebral vasospasm. When more than one aneurysm is demonstrated, the aneurysm that has bled or is about to bleed can often be recognized by clearly defined vasospasm close to its origin[4] and by an irregular fuzzy outline of its dome.

Occasionally a freshly ruptured aneurysm may not be visualized despite excellent arteriographic studies. Presumably this is due to local spasm, for subsequent repeated angiography almost always shows the aneurysm. For this reason it is urged that repeat angiograms be done in such cases two or three weeks later, to be certain that no aneurysm is present. Follow-up angiograms are also advisable at a suitable postoperative interval.

Treatment

Bed rest without surgical intervention can no longer be regarded as effective treatment for intracranial aneurysms except for the very ill, comatose or elderly patient unable to tolerate an operation. Without surgery the combined immediate and ultimate mortality rate for rup-

TABLE III—MORTALITY

	*No Surgery**	*Surgery***
Age under 50	44%	11%
Age over 50	58%	50%
Comatose	83%	100%

* cf. Magladery[6]
** Intracranial surgery (temporary clip method)

tured intracranial aneurysms[6] is at least 50 per cent (Table III) and has been reported as high as 87 per cent[7]. The high mortality for surgically untreated cases is due to the frequency of fatal recurrent hemorrhage (at least 20 per cent[8]), the presence of an intracerebral hematoma (approximately 15 per cent), or progressive brain swelling (another 15 per cent) secondary to circulatory insufficiency caused by cerebral vasospasm.

Since recurrent bleeding or serious effects from progressive vasospasm are most apt to occur from the 7th to 14th day after the appearance of initial symptoms, it is wise to operate within the first week after the onset of symptoms, preferably as soon as accurate angiographic localization can be made, provided the patient is in reasonably good condition. Delays of even 24 hours may lead to fatal recurrent hemorrhage, permanent hemiplegia, or fatal brain edema that could have been avoided by earlier surgery. The minimal risk of moving a patient who has suffered a subarachnoid hemorrhage by ambulance to a hospital equipped for cerebral angiography and appropriate surgery is warranted, and indeed we know of no mishaps from such early transportation.

The selection of a given surgical procedure depends principally on three factors: the age and condition of the patient, the location and type of the aneurysm, and the judgment of the neurosurgeon.

Ligation of the internal carotid artery in the neck (neck ligation) by special clamps or other means is generally a relatively simple, safe procedure that can be highly effective for the treatment of aneurysms of the internal carotid or posterior communicating arteries. This procedure tends to lower the intra-arterial pressure within the aneurysm and to decrease the direct thrust of blood sufficiently to prevent further bleeding and to promote thrombosis within the sac. It is known, how-

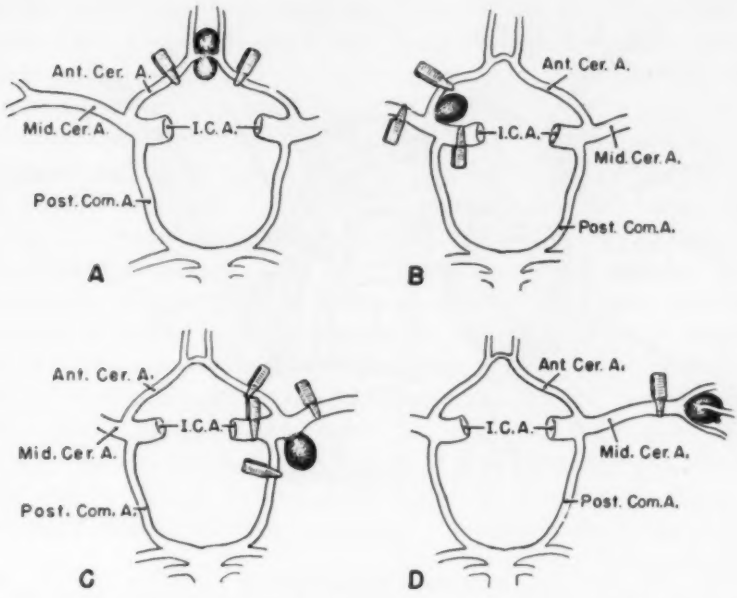

Fig. 1—Diagram illustrating typical placements of temporary miniature clips on key branches of the circle of Willis to facilitate early surgery under hypothermia of recently ruptured intracranial aneurysms.

ever, that neck ligation sometimes leads to permanent hemiplegia despite every effort to avoid or correct such a complication, and that this technique, if used when most needed, i.e., during the bleeding period, is apt to prove unsatisfactory. It is also known that aneurysms occasionally rupture fatally even after an apparently successful carotid ligation in the neck. For these reasons the author prefers direct intracranial obliteration of the aneurysm whenever possible.

Technical developments that now make the direct early surgery of ruptured intracranial aneurysms safer and easier include the use of hypothermia[9] and small removable clips*[10-12] during the operation for temporarily occluding the local blood supply to an aneurysm (Figure 1), until the aneurysm has been obliterated by permanent clips or by other means. Controlled hypothermia[13, 14] at 27 to 29° C. safely protects the brain from the effects of existing or deliberate circulatory interference and facilitates the surgical approach by reducing brain volume[15, 16].

* Kees Surgical Specialty Co., Alexandria, Kentucky.

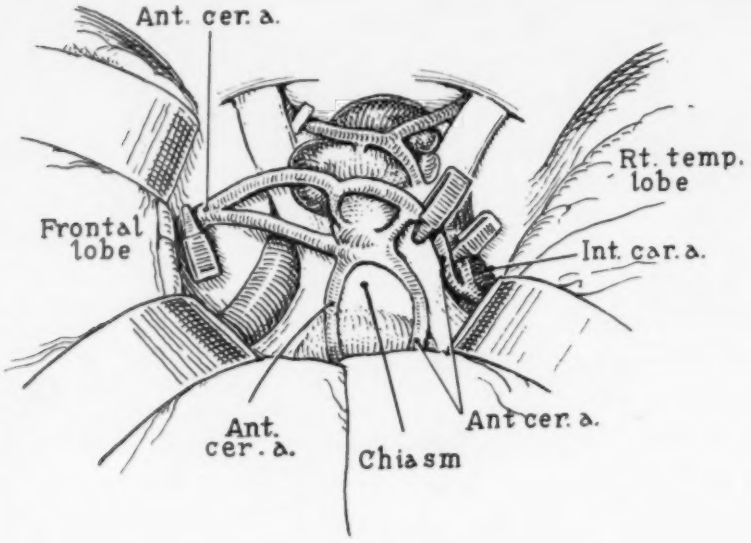

Fig. 2a

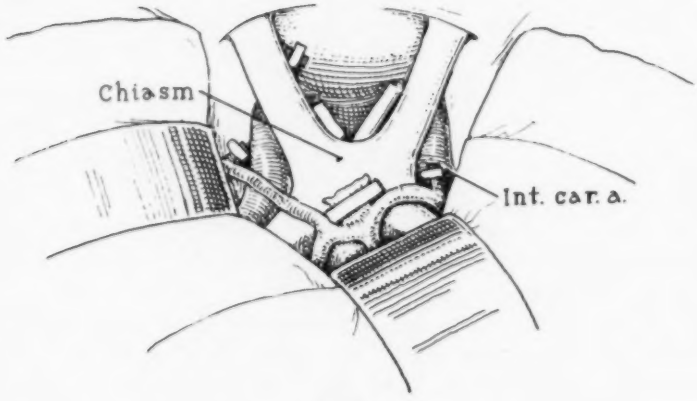

Fig. 2b

Fig. 2 (a)—Diagram prepared from color photographs taken at operation of aneurysm shown in Fig. 3. Note temporary clips on anterior cerebral arteries proximal to aneurysm.

(b)—Decompression of optic chiasm after permanently occluding and partly resecting this large saddle-bag aneurysm that enveloped the chiasm.

It also protects the brain from the effects of temporary reduction of arterial flow for periods two to three times longer than is safe at normal body temperature. Under hypothermia, temporary clips may therefore be placed on key branches of the circle of Willis for 15 to 20 minutes. This shuts down the local arterial supply to an aneurysm, as indicated in Figure 2, long enough to complete its dissection and permanent obliteration with little risk of a hazardous or fatal rupture, and avoids the additional surgery and risks formerly required for exposure and temporary occlusion of the carotid and vertebral arteries in the neck. The temporary clip technique has proved particularly valuable for the surgery of anterior communicating artery aneurysms, which are notoriously difficult to treat and do not as a rule respond well to ligation of the carotid artery in the neck. Clinical observations, postoperative angiography and careful examination of vessels in our autopsied cases yielded no evidence that the application of these temporary clips caused any vascular damage. In other words, we have not seen any example of arterial thrombosis or injury secondary to the use of these clips.

Selection of Patients

As to the condition of the patient for intracranial aneurysm surgery, those who are older than 50, those who are seriously ill or comatose by virtue of their hemorrhage, and those who are afflicted with hypertensive cardiovascular disease are obviously poorer surgical risks than younger patients (Table III) in reasonably good condition despite a fresh subarachnoid hemorrhage and developing neurological signs that indicate rather than contra-indicate prompt surgery.

Personal experience agrees with that of others in that the comatose patient can hardly ever be saved by any form of aneurysm surgery[9], although various unsuccessful attempts have been made to do so purely as a measure of desperation (Table III). It is also evident that the mortality and morbidity rates increase in almost linear proportion to the degree of preoperative morbidity and the age of a patient over 50. The sicker the patient and the more elderly he is, the less favorable are the chances for a successful postoperative result. It is all the more important therefore to try to save patients of the younger age group, provided they are not comatose, by radical intracranial surgery. They can usually tolerate such surgery well and it virtually removes forever the threat of fatality from recurrent hemorrhage. Moreover, when done promptly,

TABLE IV—MORTALITY

Aneurysm	*No Surgery*	*Carotid Ligation in Neck*	*Intracranial Surgery Temp. Clip Method*	
			Over 50	*Under 50*
IC-PC	50% DP	5% S	50%	11%
MCA	90% P-D	22% P-D	100%	0
AC-ACC	90% B&B	50% S	33%	20%

DP — Parkinson,[7] D.
S — Shenkin[17]
P-D — Petit-Dutaillis[18]
B&B — Baumann and Bucy[19]

even though neurological signs are developing due to spasm or other causes, intracranial obliteration of an aneurysm can also prevent permanent brain damage.

SELECTION OF OPERATION

As already indicated, intracranial surgery is the procedure of choice for aneurysms of the anterior communicating artery (Table IV), which seem particularly prone to recurrent and usually fatal hemorrhage unless so treated[19]. Moreover, anterior cerebral aneurysms do not respond well as a group to carotid ligation in the neck[17], although there are of course individual exceptions. Many of them, finally, have large, multilobed, thin-walled sacs that envelop and compress the optic chiasm or nerves like a saddle-bag (Figures 3, 4), thus carrying a constant threat of blindness unless obliterated.

Aneurysms of the middle cerebral artery are almost but not quite in the same category, being somewhat more amenable to treatment by carotid ligation in the neck than are aneurysms of the anterior cerebral artery[17, 18].

Aneurysms of the internal carotid-posterior communicating arteries can be treated by carotid ligation in the neck with a high degree of success[17], although fatalities from rupture and permanent complications can follow this type of procedure. Although the morbidity and mortality rate is essentially the same for direct intracranial surgical obliteration of these aneurysms as it is for carotid ligation in the neck, a successful intracranial procedure practically guarantees a permanent cure and therefore seems preferable. Furthermore, when multiple aneurysms or

Fig. 3(a)

Fig. 3(b)

Figs. 3(a) and (b)—Pre- and postoperative angiograms of another case of aneurysm of the anterior communicating artery operated upon 11 days after hemorrhage. Note postoperative filling of both anterior cerebral arteries (b) and disappearance of preoperative vasospasm of anterior cerebral, internal carotid and proximal portion of middle cerebral arteries.

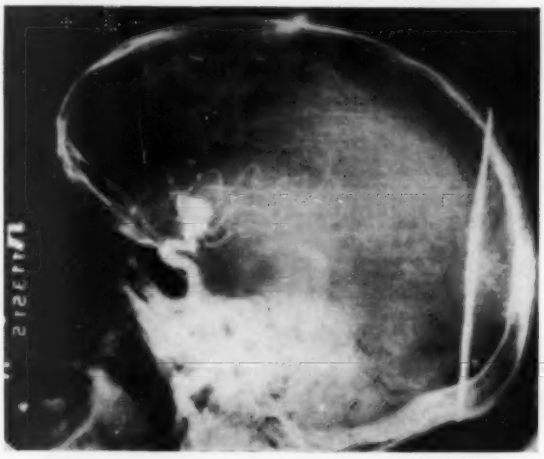

Fig. 4(a)

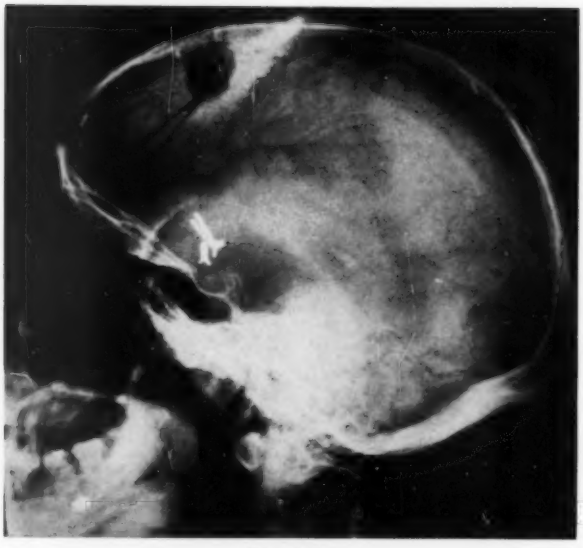

Fig. 4(b)

Fig. 4—(a) lateral angiogram and (b) postoperative film of a recently ruptured aneurysm of the anterior communicating artery treated by the temporary clip method. Three of 5 such cases with known vascular hypertension survived early obliteration of their aneurysm. The two who died were comatose before operation.

TABLE V—RESULTS

ANEURYSM SURGERY UNDER HYPOTHERMIA
WITH TEMPORARY CLIP METHOD

No. of Pts.	*1-12 Days After Hem.*	*Site of Aneurysm**	*Mortality*	*Morbidity*	*Working*
Under 50					
9	8	IC-PC	1c	0	8
3	2	MCA	0	2	1
5	4	ACC	1	1	3
17	14		2 (11.7%)	3 (17%)	12 (70%)
Over 50					
2	1	IC-PC	1	—	1
1	1	MCA	1c	—	—
3	3	ACC	1c	2	—
6	5		3	2	1

* IC-PC: internal carotid-posterior communicating
MCA: middle cerebral artery
ACC: anterior communicating artery
c = Comatose preoperatively

certain anomalies of the circle of Willis are present, intracranial surgery rather than carotid ligation in the neck is virtually imperative.

Multiple aneurysms, it should be emphasized, if not excessive in number, can be successfully treated by intracranial surgery by staged operative procedures (see RESULTS).

RESULTS

The results (Table V) of intracranial surgery with the temporary removable clip method under hypothermia do not perhaps give a true index of the value of this technique. In the first place, the five patients who died following its use were those who would probably have succumbed to any form of surgery. Three were comatose prior to operation, one died of coronary insufficiency and one of cerebral edema. In the second place, this technique has frequently permitted successful obliteration of unusually large, thin-walled, recently ruptured aneurysms, such as the saddle-bag aneurysms glued to the optic chiasm, that might well have been impossible to treat properly by other means.

Of the 23 patients in Table V, 19, or 82 per cent, represent patients in whom immediate or early intracranial surgery was performed within

one to 12 days after subarachnoid hemorrhage or presenting neurological signs. Eleven, or more than half of these cases, were operated upon within the first three days. The mortality rate was only 14 per cent in the group of 14 patients 50 years of age or younger who were submitted to immediate or early surgery, and 11.7 per cent for the entire group of 17 cases under 50. This compares favorably with mortality rates for untreated cases and for cases treated by other methods, even though many of them were not operated upon until several weeks after hemorrhage and therefore represented a better selected group of patients.

Morbidity in Table V refers to postoperative mental changes or hemiparesis resulting in inability to work.

Of the 23 reported cases four patients had two aneurysms apiece. Three survived surgical treatment of both their aneurysms. Two have resumed their usual work or activity, while one is mentally retarded. The fourth is well and awaiting intracranial obliteration of a contralateral aneurysm.

Two pregnant patients successfully withstood intracranial clip obliteration of their aneurysms under hypothermia shortly after fresh subarachnoid bleeding, with subsequent normal term delivery of healthy infants. At the time of this surgery one was in the third month and the other in the seventh month of pregnancy.

Conclusions

1. Early intracranial surgery for the treatment of aneurysms of the circle of Willis or its branches is indicated, preferably within six days after presenting symptoms, whenever the age and the condition of the patient permit.

2. Satisfactory results may be expected in patients below 50 years of age who are in reasonably good physical condition, less good results in patients over 50 and poor results in those who are comatose, regardless of their age.

3. Special removable clips for temporary local intracranial reduction of blood flow at the site of the aneurysm facilitate aneurysm surgery, particularly for the isolation and permanent obliteration of recently bleeding anterior communicating artery aneurysms.

4. Despite the value of this technique it is not the author's intention or practice to advocate its application in every case of intracranial aneurysm. Each patient is treated according to the method deemed most suitable for that particular case.

The author gratefully acknowledges permission to include 3 patients for whom this technique was used by Doctors John E. Scarff, Joseph Ransohoff, and James W. Correll, respectively.

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NEUROLOGICAL AND RADIOLOGICAL MANIFESTATIONS ASSOCIATED WITH SPONDYLOSIS OF THE CERVICAL AND LUMBAR SPINE*

JOSEPH A. EPSTEIN AND BERNARD S. EPSTEIN

THE purpose of this report is to analyze the clinical syndromes caused by injury to the spinal cord, nerve roots and cauda equina by spondylosis of both the cervical and lumbar spine. This disease originates as a degenerative lesion of the intervertebral disc, involves the adjacent vertebral margins and excludes the alterations of osteoarthritis. The latter is produced by an inflammatory reaction affecting the posterior apophyseal articulations, the only joints lined with synovial membrane. The involvement of Luschka's joints (unco-vertebral, covertebral) is a debatable issue. Since we have found similar alterations in the uncovertebral area of the cervical region to correspond to identical abnormalities in the corresponding margins of the vertebrae in the lumbar region causing foraminal constriction, we are reluctant to ascribe these changes to a distinct anatomical entity of this character. By far the most common alterations caused by spondylosis occur in the anterolateral aspects of the vertebral column, and may not be associated with any specific complaint. However, when the spurs and ridges protrude into the spinal canal or foramina from the posterior or posterolateral aspect of the vertebrae, pressure effects and circulatory disturbances involving the spinal cord, the nerve roots and the cauda equina result.

These changes become manifested clinically by syndromes directly referable to the portion of the neural axis involved, and during the past ten years, a recognizable clinical syndrome has been defined, especially in the cervical region. Heretofore, the tendency has been to overlook the effects of such anatomical changes in the cervical spine and these patients have been variously categorized into the syndromes and variations of amyotrophic lateral sclerosis, multiple sclerosis, progressive

* Presented at the meeting of the Section on Orthopedic Surgery, November 10, 1958.
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lateral sclerosis and tumors or degenerative diseases of the spinal cord. In addition, the co-existence of spondylosis and any of the above-mentioned disorders now appears to be a very definite possibility.

Involvement of the roots of the cauda equina by this process has not yet been fully appreciated. This syndrome may produce profound disability both because of pain, which is the most conspicuous feature, and because of weakness, sensory disturbances and severe sphincter involvement. The syndrome has been often confused with that caused by herniation of the intervertebral discs and by neoplasms.

As in the cervical region, two problems may be found in association with each other, a herniated disc at one level and spondylosis at another. To treat just one abnormality and to ignore the other is an error which results in further disability as time progresses. The dorsal intraspinal protrusion caused by spondylosis may be important in patients with radicular syndromes of obscure etiology in which intervertebral disc narrowing with eburnation of bone and marginal lipping is minimal on plain roentgenograms. Indeed, the true extent of such spurs may not be identified because they contain unossified osteoid tissue. Under such circumstances, the diagnosis is facilitated by myelography.

We have also observed at operation in the lumbar region of certain patients that the ligamentum flavum, neural arches and articular processes may be abnormally thickened, producing a definite stenosis of the spinal canal. The significance of these changes was initially not fully appreciated. A narrow canal of this character, either developmental in origin as suggested by Verbiest[1] or caused by osteoarthritis of the posterior articulations, may render individuals so disposed more susceptible to critical injury of the neural structures by spurs and disc protrusion of relatively minor degree.

As age advances, the loss of turgescence of the nucleus pulposus with thinning and outward bulging of the annulus fibrosus produces an abnormal strain on the spinal ligaments, loosening their connection to the periosteum at the ring epiphysis. This results in an elevation of the periosteal layer. It was clearly shown by Collins[2] and Hadley[3] that osteophytes are constructed of new periosteal bone laid down between the elevated periosteum and the original corticalis of the vertebral bodies. The new bone is initially coarsely trabeculated or compact and only later becomes cancellous, containing marrow spaces communicating with the marrow cavity of the vertebrae. While bone matrix is nor-

mally calcified as soon as it is formed, there is evidence from the study of undecalcified sections that the calcium load of the marginal area of newly formed bone does not reach an immediate maximum. In such patients operation may disclose formidable ridges which were not suspected in initial spine films.

Indentation of the spinal cord occurs opposite the ridges on the anterior surface of the cervical canal caused by the protruding disc tissue and marginal osteophytes. Interference with the circulation of the cord by compression of the anterior spinal artery and the major radicular arteries further complicates the problem. Both are regarded as significant in the production of myelopathy.

In spondylosis, narrowing of the intervertebral disc space and sclerosis of the vertebral margins occurs with the vertebral bodies lying in closer apposition. This results in approximation of the pedicles, reducing the cephalocaudad diameter of the foramen. Osteophytes projecting backwards from the vertebral margins or spur formations projecting anteriorly from the posterior articulation further contribute to foraminal constriction and nerve root compression.

When the disc becomes thin, the lower vertebra is wedged forward because of the incline to the plane of the posterior articulation, resulting in a reverse spondylolisthesis, further decreasing the anterior-posterior diameter of the foramen. Along with this subluxation, the upper tip of the lower articular process projects into the opening. Associated hyperplasia or ossification of the ligamentum flavum encroaches still further upon this critical reserve space. It should be noted that at this level the disc forms the lower anterior border of the foramen and any protrusion in this area results in acute compression of the nerve root against the pedicle, very often with fibrotic changes and adhesions developing in and about the nerve[3].

Persistent pain and disability with reflex and sensory alterations of an irreversible nature may possibly be referred to changes of this character. Pain may also be the result of strain upon the ligamentous structures of the articulations. Nerve root pressure and deformity occurring in the intervertebral foramen cannot at times be adequately visualized by contrast media within the dural envelope.

The present report will include the 12 cases originally presented by Epstein and Davidoff[4, 5] in 1951 and 1953. Seventeen new cases have been added, with a critique of current thought in the changing inter-

pretation and management of these syndromes. The structural alterations have already been described in detail in an earlier presentation[6, 7].

Cervical Spondylosis

There were 15 patients with symptoms referable to the cervical spinal cord and nerve roots. Their ages varied from 42 to 69 years. Symptoms had been present from four months to approximately eight years.

Trauma apparently played a provocative role in three patients. One person lifted a heavy object to his shoulder; suddenly noted severe pain in the back of his neck spreading down his left upper limb and later into the precordial area, simulating angina pectoris. During the course of his illness, hyperextension of the neck, coughing and carrying weights in the left hand reproduced these symptoms. Repeated electrocardiograms were negative. A woman suspected of having multiple sclerosis for eight years spontaneously developed severe pain radiating from her neck into her left hand, with numbness of the first three fingers, followed by an exacerbation of her former complaint. In the remaining patients, pain was never disabling but was recorded as annoying or disturbing, varying from burning paresthesias to feeling of coldness in both lower limbs. An ache was described in the cervical and interscapular region of insufficient severity to be of diagnostic importance. The burning pains present in four patients involving the trunk and low extremities were similar to that associated with known intramedullary cord disease.

Symptoms involving the lower extremities were the first to appear in ten patients. These consisted of the gradual onset of unsteady gait, with signs of spasticity and weakness. The Romberg sign was frequently positive. They had difficulty in tandem walking, showed hyperreflexia with clonus as well as pathological reflexes. Abdominal reflexes were lost or depressed in the majority of cases.

Symptoms first appeared in the upper limbs of three patients, simultaneously in both the upper and lower extremities in two. There was evidence of weakness, stiffness of the fingers, numbness and a definite inability to perform fine, complex movements. Patients also complained of disagreeable shock-like sensations, pins and needles and hypersensitivity of the skin. Restricted and painful movement of the neck was present in only two patients, with evidence of acute nerve root

compression. In only one was there a complete absence of pain.

The course of the illnesses was marked by progressive disability. All four limbs were ultimately involved in the majority.

Sphincteric disturbances occurred in six. These were minor, such as a delay in initiating the urinary stream in the older men, suggesting prostatism.

Weakness of the upper extremities was associated with atrophy of the small muscles of the hands. Occasional hyperactivity of the radial and finger flexor reflexes with inversion was found in the presence of absent or depressed reflexes at the biceps and triceps levels. Fasiculations were observed in three patients. Sensory levels to pinprick, touch and temperature were poorly defined at the lower or mid-cervical region in five patients, being distributed over the thoracic area in the remainder. Only two patients showed no sensory abnormality, despite the fact that they complained of paresthesias and showed other neurological changes. Both had advanced degrees of spondylosis, one with a complete block on myelography at the C-6-7 interspace.

Position and vibration sense were markedly depressed in seven patients. When found, these alterations were usually more profound than the deficit noted to pinprick and touch. Saddle anesthesia was never demonstated. The lack of coordination manifested in the majority of these patients was disproportionate when compared to the evidence of weakness, spasticity and sensory deficit.

Plain roentgenograms of the cervical spine disclosed evidence of marked spondylosis at single or multiple levels, with evidence of foraminal constriction and alterations in the shape of the vertebral bodies and the height of the intervertebral discs. The C-5, C-6 and C-6, C-7 interspaces were implicated in all cases, the C-4, C-5, with lesser frequency and only rare alterations of significance were found at higher levels. On these films, bony projections extended from the posterior border of the vertebrae into the spinal canal, effectively narrowing the anteroposterior diameter and compromising the foramina. The full extent of these posterior projections could be fully appreciated only on myelography because of insufficient density of the ridge tissue on many of the plain roentgenograms.

The curvature of the spine and the mobility were affected primarily in those patients with multiple joint involvement. Signs of apophyseal joint alterations were not found either on the x-ray studies or at sur-

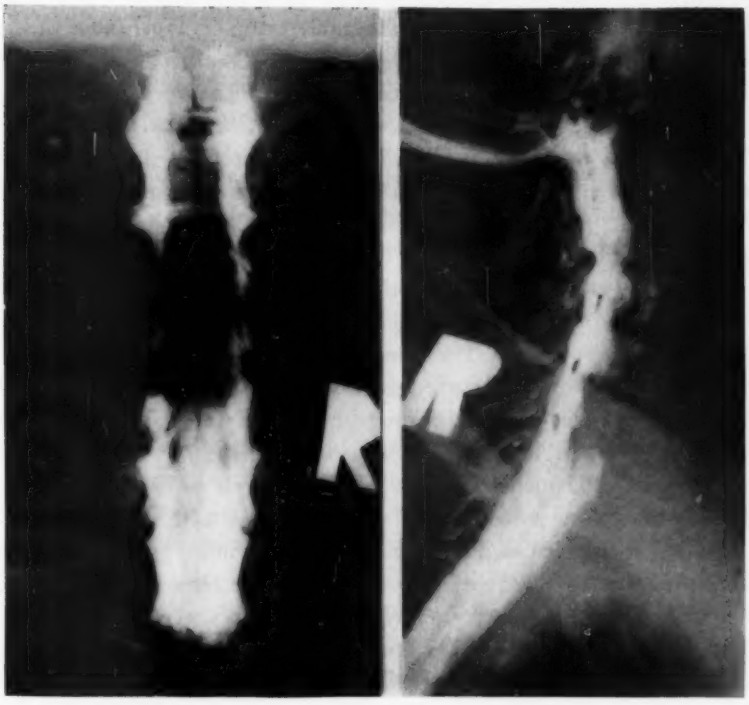

Figure 1A

Figure 1B

Figure 1A—Cervical Pantopaque myelogram with ridge defects at the interspaces between the 4th, 5th and 6th cervical vertebrae. Note the indentation into the lateral aspects of the Pantopaque column, as well as the deficient filling at the levels of the respective intervertebral discs.

Figure 1B—Oblique cervical myelogram showing indentation into anterior aspect of Pantopaque column due to spondylitic ridging. The posterior indentations are caused by the yellow ligaments.

gery. Myelography was performed in all cases by means of the lumbar route. The most frequent abnormality was a series of horizontal defects at the level of the intervertebral spaces with deformity of the axillary pouches corresponding to the ridges of bone and protruding disc tissue (Figure 1A). In one patient, the protruding ridge was large enough to cause a complete block at the level of the sixth interspace. A second similar block was then demonstrated at the third interspace by means of a cisternal injection of Pantopaque. In addition to the defects caused by

the anteriorly situated ridges, a second group of defects could be seen in the posterior quadrants of the spinal canal caused by protrusions of the yellow ligament (Figure 1B). Hyperextension accentuated these defects and further narrowed the spinal canal.

A manometric block was present in one patient, partial in two and present only with the cervical spine in the position of hyperextension in two additional patients. The protein content of the spinal fluid varied from 35.5 milligrams per cent to a maximum of 177.5, the average being between 40 and 60 milligrams.

Operation was performed in the prone position in all except one patient. It was primarily a decompressive procedure with laminectomy of two to four vertebrae. The bone removed included as much of the proximal portion of the foramen as was feasible. Care was taken never to insert the lower lip of the rongeur beneath the lamina, to avoid crushing the underlying cord against a ridge. The dura was opened and the denticulate ligaments cut at all exposed levels to reduce tethering of the cord[8]. In one patient, a fresh, extruded fragment of fibrocartilage was found at the apex of a bulge caused by protruding osteophytes and disc tissue. Remarkable relief of pain followed its removal. No attempt was made to remove anteriorly-lying osteophytes, the hazard to the spinal cord being too great. Unco-vertebral osteophytes in the lateral foraminal areas could be excised with safety. Hemorrhage was difficult to control in the face-down position. Epidural veins were engorged, and obscured the numerous fine and coarse adhesions binding the roots to the surrounding tissues. Visualization was poor under such circumstances, and surgery difficult.

There were three deaths in the series. Only two could be related to the immediate postoperative period. Poor results were noted in three patients; two patients showed no change. Six had good results; one an excellent response with complete relief of symptoms.

One patient died three days after operation with signs of hematomyelia involving the cervical and upper dorsal spinal cord. A second died 22 days postoperatively with thrombosis of the basilar artery. A third patient was operated upon under desperate circumstances and died in a respirator with a transverse cervical myelopathy, signs being evident before surgery. A serious postoperative complication in one patient was thrombosis of the central retinal artery. This could be attributed to pressure upon the eyeball with the patient in the face-down position.

The one patient operated upon in the seated position did unusually well, and the operation itself was far simpler to perform because of minimal bleeding and better visualization of anatomical structures.

Poor results included one patient who remained tetraplegic after myelography. The patient with both multiple sclerosis and spondylosis improved temporarily; however, signs of progressive deterioration were noted approximately nine months after operation. A third patient in this group improved for four months, after which he sustained a cervical spine injury in an automobile accident with an acute recurrence of his former neck and precordial pain.

Six patients, followed up to two years, showed improvement in performance capacity, with a decrease in spasticity and arrest of the progression of the disease. In only one patient was an excellent result obtained. He had a brief history of only ten months' duration, and the pathology consisted primarily of unco-vertebral osteophytes with foraminal constriction.

One is left with the impression that in all patients with this disorder, a maximum effort must be made to exclude the possibility of co-existent disease and not to ascribe all of the neurological abnormalities to the alterations in the cervical spine. A meticulous neurological evaluation is mandatory in order to recognize these patients with degenerative disorders of the spinal cord and brain stem and those individuals with spinal cord tumors or herniated discs[9, 10]. The latter possess many features in common with the present syndrome and it may be impossible to distinguish them, even with myelography.

An adequate trial of conservative management would include immobilization of the neck by means of a collar and cervical traction in a position of slight forward flexion. This posture assures the maximum anterior-posterior diameter of the spinal canal. Physiotherapy and change of occupational stress should be integrated into the over-all program. If, despite these measures, disability progresses or reappears after a period of improvement, surgical decompression is indicated. Recent encouraging reports by Allen[11] and Mayfield[12] indicate that it is possible to remove the anteriorly situated ridges by means of specially designed curettes and rongeurs with better results than may have otherwise been anticipated.

The results recently reported have been encouraging for periods of from six to nine months, after which time a significant number of

patients have shown regression, indicating that ultimate improvement may be doubtful[13]. Unfortunately, many patients are first seen when advanced in age and disability, making diagnostic procedures difficult and surgery dangerous. Where there is evidence of appreciable myelopathy of long duration, these alterations are for the most part irreversible. Younger patients with the least evidence of cord involvement appear to benefit, more so if only one interspace is implicated. Poor responses may possibly be caused by the persistence of vascular alterations and adhesive arachnoiditis. Stabilization of the cervical spine by means of fusion may prevent further structural deformity and minimize abnormal mobility, reducing stress at both the vertebral synchondrosis and the posterior articulations. Whether this will limit the re-formation of osteophytes can only be conjectured.

Lumbar Spondylosis

There were fourteen patients in the present series. Eight were men and six were women. The age varied from 29 to 66 years. The majority were in the fifth and sixth decades of life. In all, low back pain was the outstanding complaint, with radiation down one or both lower extremities in a radicular pattern. The duration of symptoms was from three weeks to as long as ten years, with one patient presenting recurrent difficulty over a twenty year period. Four patients had symptoms between one and three years, five less than eight months. During the three to four months preceding surgery, disability had increased despite bed rest, traction, the use of various supportive devices and physical therapy. In view of the absence of any sustained relief, all were subjected to myelography and surgery.

Symptoms were bilateral in nine patients. In three, pain was more intense on one side than the other. The remaining five patients had unilateral extremity pain dominating the clinical picture. In these, the syndrome could not be differentiated from the usual picture of a herniated intervertebral disc. Trauma could conceivably have been a precipitating factor in four patients, lifting a heavy object being the immediate cause of distress in three, a fall with a back injury in one. Most patients were unable to recall a specific event. Exacerbations had occurred spontaneously and with such frequency over an extended period that no useful information could be obtained in this regard. The majority of patients complained of increasing distress on standing and

walking, on sitting and during postural changes. Coughing, sneezing and straining caused pain in about one-half of this group. Many had achieved some measure of relief with prolonged bed rest, except for one patient whose symptoms were aggravated by this position. Exacerbations were abrupt in onset, rapidly progressing to total disability in those with bilateral symptoms. Occasional burning pain was present, spreading into the extremity from the low back area. There were complaints of numbness and coldness, as well as severe, spasmodic cramping sensations in the low back, posterior thigh and calf areas. Changes in sphincteric function were observed in four patients, all with bilateral difficulties. Such alterations extended from occasional stress incontinence to total loss of rectal and bladder control in one patient. Difficulty in initiating the urinary stream was a common disorder in those patients who did not progress to the greater state of disability.

Weakness of the distal musculature was present in the lower extremities of all patients with evidence of atrophy and occasional fasiculations. Bilateral foot drop was observed once. Reflexes were depressed to absent in the lower limbs, the ankle jerks being most seriously affected. Sensory changes were less conspicuous, being absent in five patients but evident in the remaining members of this group, the deficit involving either single or multiple dermatomes in an irregular pattern. Pain and touch were more seriously disturbed than appreciation of position and vibration. The defect was found in the L-5 and S-1 dermatomes and included the remaining sacral areas, depending upon the severity of nerve root compression. These findings varied from a mild subjective change to saddle anesthesia. Sensory alterations did not always follow the change in reflex status and were often disproportionate. The Lasègue maneuver was usually positive during acute exacerbations, where loss of lumbar mobility, flattening of the lumbar curve and spasm of paravertebral muscles were noted. Where less acute, this test was surprisingly negative, even in the presence of a considerable neurological deficit and varying discomfort.

Roentgenograms of the spine disclosed evidence of spondylosis at either single or, more often, multiple levels in the lower lumbar region. Interspaces were narrowed and osteophytes at the vertebral margins encroached upon the intervertebral foramina. Spondylolisthesis without spondylolysis was evident in the more advanced cases. In one, the body of L-4 was dislocated anteriorly upon the body of L-5, a complete

Figure 2A

Figure 2B

Figure 2C

Figure 2A—Lateral roentgenogram showing a spondylolisthesis with forward displacement of the 4th on the 5th lumbar vertebra. Note the impingement of the posterosuperior aspect of the 5th lumbar vertebra against the intervertebral foramen and consequent alteration in the foraminal contour. The anteroposterior diameter of the canal is narrowed.

Figures 2B and 2C—Posteroanterior and lateral Pantopaque myelogram reveals a complete block at the level of the 4th interspace. Note the difference in the depth of the spinal canal at the intervertebral levels as compared with that at the midportions of the vertebral body

block resulting within the spinal canal (Figure 2). Plain roentgenograms were described as "not remarkable" in two patients aged 29 and 49; an isolated spur being noted in another. Nevertheless, in one patient considerable indentation of the spinal canal was evident on myelography, the vertebral canal being obstructed in the presence of minimal abnormality in initial studies.

Evidence of a complete transverse block at single or multiple levels was apparent in three patients, incomplete in five; axillary pouch deformities being present in the others. The oil would characteristically pool in the hollow of the dorsal aspect of the vertebral bodies, being broken by the ridges formed by protruding disc tissue and osteophytes and yielding a stepladder or "washboard" effect. In lateral exposures, the oil formed a teardrop or lozenge-shaped globule, coming to a point. A toothed pattern was seen in the anterior-posterior projection, presumably caused by multiple nerve roots projecting into the narrowed column of oil. The defects outlined the various bulges into the spinal canal at the level of the interspace, pinching off the column of oil against the overlying lamina and yellow ligaments investing the canal (Figure 3 A and B). In six patients, the alterations in the axillary pouches at the level of the interspace were the primary abnormalities. There was loss of the normal tented appearance of the axillary profile, leaving an irregular defect extending towards the midline (Figure 2B, 3B). The third, fourth, and fifth interspaces were the sites most seriously affected.

In the presence of more complete narrowing of the canal, these defects crossed the midline, producing a complete block. During myelography we attempted to insert the lumbar puncture needle above the level of the suspected lesion. However, in two cases it was inserted below the lesion, and in one a Froin's syndrome was present, with xanthochromic spinal fluid that clotted on standing. The protein content of the fluid was 180 and 190 milligrams per cent. Often, no fluid could be obtained when the needle was inserted at either the L-4-5 or L-3-4 interspace. In these cases, insertion of the needle at a higher level was successful, advanced changes at the lower interspaces making it impossible to enter the dural sac.

Spinal fluid protein was normal or slightly elevated in the remaining patients where a lesser degree of obstruction was present, and where the needle had been inserted above the level of greatest pathology.

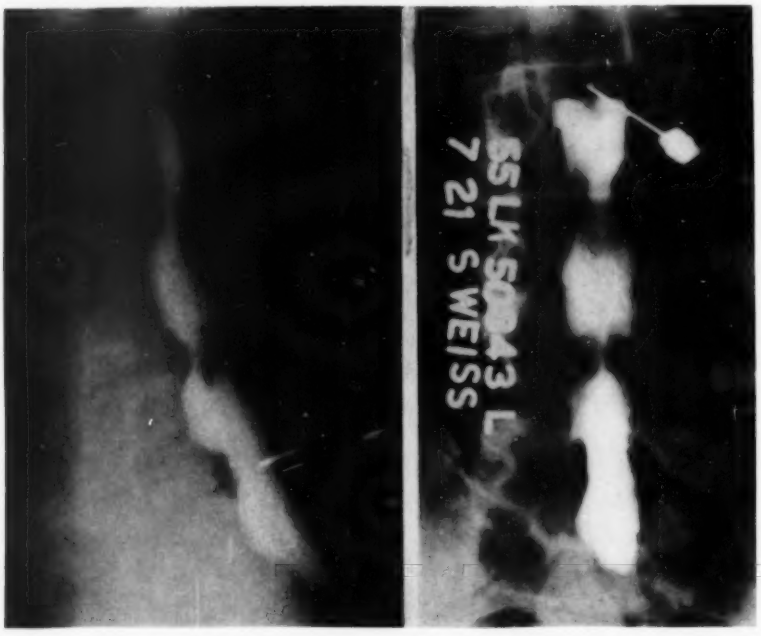

Figure 3A

Figure 3B

Figure 3A—Lateral myelogram with patient supine. Note the indentations into the anterior aspect of the Pantopaque column at the intervertebral disc levels. There is also an indentation into the dorsal aspect of the canal at the 4th lumbar interspace.

Figure 3B—Anteroposterior erect myelogram with horizontal defects at the 3rd and 4th lumbar interspaces. Note that the indentation into the anterior aspect of the Pantopaque column at the 5th lumbar vertebra has not resulted in a corresponding defect in the frontal projection.

Operation consisted of a decompressive procedure and was dictated by the severity of the alteration observed on myelography. It was performed in the crouch position in all patients. It was of considerable interest that the plain spine films, as in the cervical area, did not accurately indicate the extent of the ridge of tissue that traversed the canal. Myelography outlined the size and the type of the defect, and was far more reliable as a guide in planning the operation. A complete laminectomy was mandatory in those patients manifesting partial or complete block. Every effort was made to spare as much of the articular

facets as possible. The success of the procedure appeared to depend on the adequacy of the decompression provided by removal of laminae, yellow ligament and bony structure about the intervertebral foramen, as well as by the removal of the underlying ridges, if at all feasible.

In three patients of this group, a definite malformation accompanied the above described spondylosis. There was tremendous thickening of the laminae with the pedicles appearing closer together than normally encountered, the combination resulting in a narrow canal of the type described earlier as developmental[1]. In this group, the facets and articular processes were quite prominent and approached the midline, almost touching the spinous process and leaving very little laminae in between. This made surgical decompression an extremely difficult mechanical maneuver. It was evident that a moderate bulging of disc tissue or an area of spondylosis could further narrow a canal of this type to the point of critical nerve root compression. The similarity to the spine in achondroplastic dwarf was striking[14]. Ridges of bone or of dense fibrous tissue, when accessible anterior to the nerve root or to the theca, were removed, using pituitary rongeurs or sharp curettes. All degenerated disc tissue within the interspace was extracted. In the unusually narrow canals, where it was impossible to retract the nerve root or the dural envelope safely, a dorsal decompression by means of laminectomy and foramenotomy was all that could be achieved.

Frank extrusion of disc tissue, lying entirely free within the vertebral canal, was found in only two patients. In one, the patient's illness was acute in onset, only three weeks in duration. The patient exhibited a profound neurological deficit with evidence of a complete block on myelography. The second patient similarly had an acute onset of symptoms with severe disability and a partial block on myelography. The quantity of extruded material was small in both cases, in the aggregate measuring less than one cubic centimeter, but sufficient in amount to narrow further an already stenosed canal beyond the tolerance required by the enclosed dural envelope and cauda equina.

Postoperatively, there was early and at times striking relief of the severe radicular pain, often noted within the first 24 hours. The alteration in character of pain was appreciated often during the immediate postoperative period. Where pain recurred, it was rarely of the disabling character present before surgery, except in one patient who, approximately one year postoperatively, experienced a gradual return of his

former distress. This patient presented the longest history of low back pain and extremity pain in the entire group. While his initial response was gratifying, his subsequent course was disappointing.

Sphincter disturbances of an appreciable degree preoperatively were a poor prognostic sign. It usually remained as a serious problem throughout the postoperative course, both rectal and urinary incontinence persisting in two of the three patients so afflicted prior to surgery. After nine months in the one woman with this problem, adequate function was restored. One patient, with only slight difficulty preoperatively, developed severe disability in this regard after surgery. Improper use of rongeurs, with nerve root compression at the time of laminectomy, resulted in a permanent loss of sphincter function, emphasizing the need for a complete understanding of the bony architecture and the soft tissue pathology. The insertion of a metallic instrument into the narrow canal, such as a retractor or the tip of a rongeur at the time of laminectomy, can further compress an already severely traumatized nerve root to the point of complete interruption of function.

Postoperatively, improvement in sensation, reflex and motor power was noted in varying degree and no specific pattern could be defined. Those with a shorter duration of symptoms and a less severe deficit had better restitution of function. With relief of the disabling pain, the majority of these patients returned to former or restricted activity of variable degree. The reflex status was slow to improve and in no way related to functional capacity. There were four excellent results in this group with restoration of former activity; four good responses with return to useful functional capacity, with minimal restrictions. Three modest responses were noted with persistence of varying pain and restriction of activity, yet with appreciable improvement. The three remaining patients must be regarded as failures, difficult if not impossible to rehabilitate adequately, two because of sphincter dysfunction, one because of recurrent, intractable pain. Rehabilitation has been facilitated by reorganization of the lives of many of these patients, reducing occupational strain and restricting activity commensurate with functional capacity. With these limitations approximately 70 per cent of these patients have been restored to productivity.

There were no deaths in this series. The patients have been followed for periods of from six months to seven years, the average interval being from two to three years.

Summary

In spondylosis, injury to the spinal cord and nerve roots is caused by excessive narrowing of the vertebral canal and intervertebral foramina. Circulatory insufficiency may play a contributory role. Trauma is poorly tolerated by these patients and may cause abrupt neurological changes. Symptoms are progressive in nature and may be confused with degenerative disease of the spinal cord, especially multiple sclerosis and amyotrophic lateral sclerosis. Spinal cord tumor and herniated disc may produce symptoms difficult to distinguish even by means of myelography. Co-existence of primary neurological disease with spondylosis is now recognized as a serious diagnostic problem.

In the cervical region, there is early involvement of the spinal cord with the development of awkwardness of gait, spasticity and frank ataxia in the lower extremities. Numbness of the hands, atrophy and loss of fine coordinated finger movements usually follows. Signs may eventually spread to involve all four extremities. Pain is not a conspicuous feature and may be entirely absent. Reflexes are depressed in the upper limbs, hyperactive in the lower extremities and at the wrist levels, with depression of position and vibratory sense of variable degree. Pain and touch may be less involved, sensory levels poorly defined. Babinski signs are frequently found. Sphincter alterations are rare.

In the lower spine, pain is a conspicuous feature, involving the lower back and spreading down one or both extremities in a radicular pattern. In advanced cases, sphincter function may be seriously compromised: a grave prognostic sign. Mobility of the back is restricted, reflexes are depressed to absent; sensory changes may involve multiple dermatomes. Weakness and atrophy may be profound.

Conservative treatment may provide temporary relief by means of immobilization and traction. With an advancing neurological deficit despite such measures, decompression by means of laminectomy and foramenotomy, with removal of osteophytes and ridges anterior and lateral to the canal when possible, may provide some degree of improvement in from 50 to 70 per cent of patients. Congenital narrowing of the canal in the lumbar region appears to be a definite clinical entity. In this group of patients, minimal protrusion of disc tissue or spur formation in the ventral quadrants of the spinal canal results in painful and disabling nerve root compression. Decompressive laminectomy is the treatment of choice.

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THE RISE OF SYNTHETIC DRUGS IN THE AMERICAN PHARMACEUTICAL INDUSTRY*

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THE earliest concept of the use of drugs for the treatment of disease arose long before recorded history, but the search for synthetic chemical agents for this purpose began to assume its modern form only about a century ago. Yet, like the flowering of a plant, there was much quiet growth long before the first blooms appeared.

Man has always shrunk from the pain of illness and the terrors of death. His attempts to postpone the inevitable led to a groping search for something which would be helpful. Thus the very idea of a medicine was created—"born of need", Claude Bernard said. "From the first time anyone was ill, man went to his aid and sought to cure him with whatever came to hand. From its cradle medicine has therefore been applied science mixed with religion and with the feelings of sympathy that man experienced one for another." Primeval man found himself in a world hard to understand. In his search for explanations he ascribed diseases to supernatural visitations. Hence, it was logical that the priest should be the first "physician". His role was two-fold: to prevent the demons of darkness from possessing man and, failing in this, to drive out the evil spirits which had invaded the body. Medicine was witchcraft, white magic – locked like Ying and Yang in eternal conflict with the black arts. Its methods were largely religious; its therapy, mystical. In fact, the original meaning of the word "pharmacy" signified a form of witchcraft involving drugs to produce death.

There is a definite relationship between the concept of disease and the methods adopted to counter it. As long as the old idea held that disease was due to malign influence from without, magical methods of treatment were, without question, perfectly appropriate. With the con-

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cept that disease is a reaction of the body itself to changes in the external and internal environment, it was finally realized that rational therapeutics must take the form of aid to the natural defenses of the body. But, millenia were to pass from the incantation of a witch doctor to the deliberate, coordinated research which leads now to the discovery of new synthetic therapeutic agents.

At the beginning of recorded history man had become dissatisfied with fantasies as explanations for the perplexing questions of sickness and therapy, so in the Near East and Egypt the search that was to become medical science began over seven thousand years ago. There were no independent sciences of chemistry, biology or physics—it was only a single quest for knowledge. In the Nile Valley medicine had its first fine flowering. From the Ebers and other papyri we know that the Egyptians used many therapeutic agents which were, as they were to remain for ages, largely of plant origin. Botanicals were the mainstays of the physician-priest's armamentarium, augmented by some animal products and a few minerals. Around the temple courts a rudimentary chemistry developed in which a few inorganic chemicals were used. Indeed, sulfur, iron salts, magnesia, slaked lime, soda and nitre recorded in Egyptian medical manuscripts still appear in our present pharmacopeias.

The intense curiosity of the Greeks, who studied avidly every aspect of the living and non-living alike, advanced medicine through the time of Galen, about 200 A.D. During this period pharmacy and medicine were not separate entities but rather both were the province of the physician and his assistants, who gathered herbs and barks to prepare from them the decoctions used for treatment. Galen himself was renowned not only for his purely nosological studies, and as the founder of experimental physiology, but his developments in preparing plant extracts were so extensive that even today pharmacists refer to extracts of botanicals as "galenicals". In his period, following the principles of Hippocrates, diseases were looked upon as disturbances of the body and every effort was made to approach therapy rationally, rather than mystically.

With the fall of Rome, progress in Western Europe practically ceased for nearly 1000 years, but in Egypt and the Near East the ostracized Nestorian Christians continued to practice and teach in the Greco-Roman tradition. When the green standard of the Prophet swept

westward out of Arabia, his followers carried medical knowledge beyond the Pillars of Hercules. While Europe was steeped in a newer mysticism– rying to drive out disease demons with amulets, religious exercises and saintly relics–Islamic medicine, leavened with the ferment of rational Hippocratic principles, dominated from Cordoba to Baghdad. As Moslem society matured, religious inhibitions unfortunately retarded progress in medicine proper but did not prevent the creation of hospitals and the development of pharmacy and alchemy. The practice of pharmacy became distinct from medicine. It was regulated and systematized in official books of formulae. In fact the first London Pharmacopeia was openly based largely on a Moslem formulary. The Arabs collected earlier Greek knowledge of chemistry and supplemented it with developments of their own. Medical training was rigorous and, even though anatomy and surgery were shunned for religious reasons, physicians were all schooled in chemistry. Indeed, many prominent Moslem physicians were also alchemists or pharmacists of note. At this time mercury, arsenic and the sulfates of copper and iron entered therapeutics.

From Spain via Salerno this knowledge seeped back into Western Europe with an influence that would remain long after Mohammedan political power had waned. Gradually this medical learning and its concepts of alchemy and pharmacy spread across Europe with increasing acceptance until the Holy Roman Emperor Frederick II in 1240 A.D. was moved to issue the first edict which regulated pharmacy as a profession for the collection, preparation, storing and selling of drugs.

In time, however, these fragments of Greco-Roman Arabic learning were shorn of their vitality and ossified into the medieval pattern of unassailable "authoritarian" doctrine. Ultimately the influence of new ideas undermined the rigid framework of Galenical logic and dogma. Then, when the fall of Constantinople brought a flood of original Greek manuscripts into Europe, the newly-invented printing press led to their widespread availability. Promptly a movement arose to return to the original precepts, and in the resulting ferment men became ready to believe what they saw and not what they read. Here and there, a few dared open revolt against "system", medieval or neo-Greek. With the flowering of the Renaissance, science once more pressed forward. In medicine Vesalius established anatomy on sound principles and William Harvey gave new life to physiology.

But from the view of our present topic, the most remarkable medical rebel of the Renaissance was the brash, egotistical Paracelsus, born in 1493. Son of an alchemy-minded physician and a former hospital superintendent, his inclination to the chemical side of medicine was to be expected. Three main principles consumed Paracelsus: a violent opposition to the ancient authorities, a disdain for the fantastic polypharmacy of his day, and a militant belief in chemical specifics for diseases. He was a bold experimenter in both the alchemical laboratory and the clinic. Through his efforts opium, mercury, lead, sulfur, iron, arsenic and copper sulfate were entered into the Pharmacopeias. He introduced mineral baths and popularized tinctures and alcoholic extracts. He urged the preparation and use of simple specific formulae for treatment. His own preparations, though glorified with such romantic names as catholicons and panaceas, were nonetheless for specific complaints. Many formulae ascribed to Paracelsus are as hopelessly complex as the traditional Mithridatums and Theriacs and, hence, at complete variance with his teachings, but there is reason to believe that these may not be accurate portrayals of his own remedies. His enemies and his preposterous boasting long prevented a just estimate of his accomplishments, but it now seems evident, when freed from the cloud of his unfortunate personality, that he enriched both medicine and chemistry and may truly be looked upon as the founder of chemotherapeutics.

Thus, by the mid-1500's the classic temple of scholastic medical tradition was collapsing, but the body of scientific knowledge was not yet adequate to replace it. Hence, speculative philosophy replaced authority. Finally in the 17th and 18th centuries man began to appreciate that nature operates in accordance with discoverable laws: first physics and, later, chemistry began to flower. Even though many of the physical laws were soon grasped, men of this age did not probe so deeply into the infinite complexity of life for, while physical experiment and philosophy were in mode, biological studies were still somewhat beneath the notice of a gentleman. However, lack of medical knowledge was no deterrent to the development of new approaches to therapeutics. Discoveries in the physical sciences were grafted into medicine to create schools of iatrophysics, iatrochemistry and iatromathematics. Where the simple physical laws did not quite fit living phenomena, gaps in knowledge were neatly plugged with ingenious logic. For nearly three centuries medicine continued to stumble about in blind empiricism,

progressing largely by chance observations. During this period quacks enjoyed a heyday.

With the 19th century the stage was set for the attainment of Paracelsus' goal when chemistry would bring forth not gold but medicine. The infant American pharmaceutical chemical industry had already been launched by a firm of wholesale and retail druggists, the Marshalls in Philadelphia, who commenced the manufacture of sal ammoniac and Glauber's salt in 1786. However, progress was very slow through the first four decades of the century. True, Farr and Kunzi, a predecessor of Merck & Co., began manufacture of "pharmaceutical" chemicals at the time of the War of 1812, and the separation of the alkaloids from cinchona bark in France stimulated the production of quinine by a number of American firms in the 1820's. Still, raising and selling crude botanical drugs was the mainstay of the industry, which was dominated by the Shaker sect of Lebanon, New York, who gained world-wide fame for reliable, high quality medicinal herbs and extracts. The Tilden Company of New Lebanon was established in 1824 in this region and continues today as a respected manufacturer of ethical pharmaceuticals. Four years later, in the same year that Wohler synthesized urea, William S. Merrill opened the drug shop that was to become another honored member of American pharmaceutical industry. In this period an interesting innovation was the introduction of the sugar-coated pill.

Meanwhile, in Germany, under the stimulus of Liebig and his students, there was a tremendous upsurge in the synthesis of organic compounds following Wohler's demonstration that biologically important compounds could be made by synthetic chemical processes. In France a revolution in biological thinking and medicine itself was in the making. The vitalistic philosophies of Bichat were the fashion of the day. Life was looked upon as a mysterious supernatural phenomenon which acted arbitrarily and was largely independent of all physical laws relating to non-living phenomena. From the chemical side, Wohler's synthesis of urea was a severe blow to vitalism, but it was already tottering from the furious attacks of François Magendie and others, who firmly believed that physiological phenomena were entirely explainable in terms of physico-chemical laws. In attempting to avoid the pitfalls of the rigid scholastics and speculative philosophers before him, Magendie fell into many experimental errors of his own creation. Then Claude

Bernard became his assistant, and started the work which changed the entire course of scientific medicine and therapeutics.

Bernard was a unique combination of a profound intellect, a superb technician and a brilliant experimentalist. He perceived the deeper implications of Magendie's ideas which the older man himself had not appreciated, and transformed them into a complete philosophic concept of a new method for biological research. Through its application in laboratory animals, Bernard made fundamental discoveries that had broad application in clinical medicine ranging from treatment of carbon monoxide poisoning to safer, easier abdominal surgery. However, while his actual discoveries constituted major contributions to biology and medicine, they were not in themselves much more important than those of many others. It was the creation of the exquisite logical experimental method which led to those discoveries that made Bernard an intellectual giant of all ages.

In 1865 Bernard published his greatest contribution, a little book entitled, "An Introduction to the Study of Experimental Medicine". Here he gave in detail the reasons for his belief in the constancy of the internal environment, and codified the rules for experimental biological research. He showed, step by step, how these principles of logic were applied in making his own discoveries. Here was an agenda for future medical progress through controlled experimentation.

During the score of years which Bernard spent in perfecting his methods of experimental medicine other key elements essential to the eventual establishment of an American pharmaceutical industry were moving forward. In the 1840's the synthetic organic materials, ether and chloroform, were first employed for dental and surgical anesthesia. At this time the founding of two prominent companies in the pharmaceutical industry, Sharp & Dohme and Pfizer, took place, the first as a drugstore, the second as a bulk supplier of santonin. Important pharmaceutical industrial techniques adaptable to large scale manufacture rather than the prescription counter were beginning to appear. In 1843, when Bernard was announcing his first discoveries, Jacob Dunton began the manufacture of compressed tablets in Philadelphia, and through the 1850's and '60's the pace quickened on all fronts.

In 1856 while attempting to synthesize quinine young William Perkin in England accidentally discovered the first aniline dye, mauve. As Bernard's experimental method was to biology, so here was the

opening which led to a true synthetic organic chemical industry through whose expanding skills the molecular complexities required for drugs could be overcome. In Germany and Switzerland the significance of Perkin's discovery was quickly grasped and firms like Ciba and Bayer were founded to manufacture aniline dyes. Impatient to expand its line, Ciba took a momentous step and began independent research for new dye products in its Swiss laboratories in the 1860's.

In this country, however, industrial efforts were centering on heavy chemicals. Primitive packaging and shipping facilities restricted chemical manufacture to operations serving limited geographic areas. These limitations in distribution imposed by non-scientific considerations could not be overcome, so that the industry remained largely decentralized with growth up to 1918 reflected by additional manufacturing plants rather than larger ones. The latter half of the 19th century brought far-reaching improvements in equipment for mixing, heating, cooling and efficient recovery of end products of chemical reactions. By 1880 crude oil stills were just getting into operation although with very primitive control of the processes. Yields and purity of products were quite unpredictable, but a trickle of chemical starting materials to supplement the coal tar derivatives became available for use in synthesis of new medicinals.

In the pharmaceutical companies, efforts centered mainly on the organization of "full line" and specialty firms to supply galenicals and inorganic drugs. In 1844 Carroll Dunham Smith was established to supply homeopathic medicines which previously had all been imported from Germany. Claude Bernard's publication on internal secretions prompted John Carnrick's experimentations with galenicals and endocrine specialties which led to the founding of Reed & Carnrick. In a similar vein the late 1850's saw the rise of the Chas. H. Phillips Chemical Company, which produced Milk of Magnesia, and the William R. Warner Company.

The perfecting of a better method for making and purifying ether by Dr. E. R. Squibb, an assistant surgeon in the Navy, led to such a demand that he opened a small production laboratory in 1858. A disastrous fire on Christmas Eve left Squibb horribly burned while trying to save valuable records. In spite of the destruction of both eyelids and the loss of a hand he re-established his company with the financial backing of doctors who appreciated the importance of ether that

was free of toxic impurities and constant in potency. This reliable surgical ether was the foundation stone upon which the present diverse ethical firm of E. R. Squibb & Sons has been built.

During the years of the Civil War most existing pharmaceutical houses rapidly extended their line of products, but largely in botanical extracts together with a few alkaloid principles and the general anesthetics. This led to a pattern of distribution on a national rather than a local scale. It was not until three years after the war that a German named Bott established the Albany Aniline and Chemical Works, probably the first integrated industrial synthetic organic manufacturing operation in the United States.

During this period, Bernard's ideas on biological experimentation engaged the attention of Louis Pasteur, a practical-minded French professor of chemistry, who became an avowed disciple of the great physiologist. Pasteur was, by training and intent, a fine chemist who was diverted into biology by circumstances. A request for help from the father of a student turned his attention to the fermentation of beet sugar to alcohol. That was the demise of the brilliant young chemist but his reincarnation as a biologist. Pasteur knew next to nothing about fermentation, but he was pragmatic and was convinced that the experimental method of Bernard was the oracle that would answer any questions man put to it. He succeeded, he said, because "this marvelous experimental method . . . interrogates nature, forces it to reply and never ceases until the mind is fully satisfied." He applied Bernard's experimental principles with vigor, precision and—above all—with unbounded enthusiasm. In fact, so dramatic were his achievements that they have obscured the importance of the magnificent experimental tool which made them possible. From his studies of industrial and agricultural problems Pasteur formulated the germ theory of disease and developed the basic techniques for bacteriological experimentation. In so doing he buried forever the theories of spontaneous generation of bacteria.

As Bernard had removed various organs from animals to produce degenerative disease states which he could then study, so Pasteur succeeded in producing bacterial diseases experimentally in laboratory animals and then sought ways of curing the infections. These investigations led to the conquest of several infections, the most important to man being anthrax and rabies. In the end, Pasteur explained fermentation and putrefaction, made possible preservation of foods by "pasteurization",

developed the first experimentally produced vaccines against infectious disease and, most important, elaborated the experimental techniques which made possible the application of Bernard's methods to infectious disorders. This ability to produce infections at will was the tool which ultimately provided the route to the present virtual conquest of infection.

While these fundamental developments were going on, present American pharmaceutical companies began to appear in increasing numbers. In 1855 Frederick Stearns & Co. was organized in Detroit and pioneered complete disclosure of the ingredients in the labelling of its products. Parke, Davis & Co., founded in 1875, stressed the marketing of preparations of standardized strength. In 1876, the year that Koch exemplified his postulates in his classic study of the anthrax bacillus, Col. Eli Lilly founded his pharmaceutical company, still identified with his name and family.

Eighty years of the momentous 19th century had passed when the renowned German pharmacologist, Schmiedeberg, published his "Foundation of Materia Medica." It is of interest to note that the bulk of substances included in his text book were botanicals or extracts of active natural principles. There were just a dozen synthetic chemicals reported: ether and chloroform as anesthetics; chloral and paraldehyde as hypnotics; amyl nitrite for cardiovascular action; four external or "internal" antiseptics, carbolic acid, pyrogallol, thymol and benzoic acid; pyrocatechin and hydroquinone as antipyretics; and the first of the coal tar synthetics, salicylic acid, as an antipyretic and antirheumatic. This was pathetically small progress, it would seem, for all the years since Paracelsus; and yet, only six years before this, in reviewing the 19th century progress in industrial chemistry, Prof. J. Lawrence Smith could point to the preparation only of alkaloids such as quinine and morphine, and chloroform, chloral and ether, as medicinal products coming from American industry.

The decade of the 1880's was probably the real beginning of the present age of therapeutics. Pasteur established the concept of germs as the cause of infection, which made antibacterial chemotherapy a theoretical possibility. However, he also developed preventative vaccination for rabies, and in so doing probably delayed to some extent concerted efforts toward synthetic chemotherapeutic attack on other infectious diseases. It was, however, a major advance in treatment and the

foundation of the biologicals industry. Soon synthetic drugs began to appear in earnest: antipyrine, sulphonal, phenacetin, salol, acetanilid and many others followed in quick succession.

On the industrial side in this country the Hudson River Aniline & Color Co. was formed at Albany in 1881 and affiliated with Frederick Bayer in Germany from whom they received intermediates. Shortly thereafter in 1888 this German firm saw the value of many of the new medicinal chemicals being created from aniline and other coal tar derivatives and undertook their manufacture in Europe. In Switzerland, Ciba began similar operations.

Several fine chemical firms like Merck and the New York Quinine & Chemical Works were founded in the 1880's. However, in general, the U.S. pharmaceutical industry was not yet concerned with the new synthetics, but was immersed in problems of supplying botanicals of uniform potency and action. It was in 1888 that G. D. Searle, a Civil War veteran, whose wartime experiences had stimulated an interest in medicine, formed a company for this very purpose. The line was soon impressively extensive, but of definite galenical emphasis. Probably typical of the period, an early catalogue listed 400 fluid extracts, 150 elixirs, 100 syrups, 75 powdered extracts, 25 tinctures and 150 botanicals. Also in this year Dr. W. C. Abbott chose a different approach in an attempt to supply his profession with standardized drug extracts by commercial preparation of "active principle granules."

In this same decade Eli Lilly & Co. began the first tentative attempts at research, largely of a pharmaceutical and botanical nature. Progress was sufficient to lead to the establishment of a "Scientific Division" which was largely an analytical department, but the direct predecessor to the present true research division. Another innovation of the closing years of the century was the establishment in 1891 by a dentist, Ralph B. Waite, of the Anti-Dolor Company, now continued as the Cook-Waite Laboratories. This company offered commercially prepared dental local anesthetic solutions, first with cocaine and later with synthetics such as Novocain, which marked the founding of a new branch of the American pharmaceutical industry.

By and large, however, until the outbreak of World War I the supplying of synthetic drugs in the United States was left to foreign firms, largely German. So, likewise, was research in the field of chemotherapeutics. Not all of this was due to inertia and short-sightedness on the

part of the American pharmaceutical industry. Many essential ancillary industries were still lacking or struggling through the difficulties of their own postpartum periods. Pfaudler introduced the glass-lined tank only in 1884. By-product coking, which was an essential process to the supply of raw materials for many synthetics, was carried out for the first time at Syracuse, New York, only in 1891. The first crude instruments for controlling temperature, pressure and time of chemical reactions to give desired products were just becoming available. Electro refining of metals for corrosion resistant steel and alloys required in synthetic production was first carried out in 1908, when apparatus for working at elevated pressures was just beginning to appear. Well into the 20th century dozens of deficiencies in raw materials and equipment continued to restrain serious attempts for domestic organic chemical manufacture.

In 1898 the Curies discovered radium, and three years later it was used for therapeutic purposes. This was the first of a new kind of radioactive medicines whose number would not begin to expand until Abbott entered the field on a large scale a half century later. Meanwhile, around the turn of the century continental firms like Bayer and Ciba were establishing biological laboratories in addition to their older chemical research facilities. Almost every year saw the introduction of one or more important synthetic chemicals for medicinal use: Pyramidon, aspirin, Veronal, Suprarenin and Novocain. Endocrines enjoyed their first modern use, while the etiology of vitamin deficiencies began to unfold as Eikmann discovered the cause of beri-beri.

Until 1910 practically all the synthetic drugs of real value, except for some topical antiseptics, were useful not because they attacked and eliminated the cause of disease but because they modified the discomfort which the patient experienced from the disorder. They were symptomatic remedies in that they reduced fever, alleviated pain or brought sleep to "knit the ravel'd sleeve of care". Then another long-hoped-for medical triumph was secured through Bernard's kind of experimental approach. The vision of chemical cures for infectious disease had tantalized man for centuries. Paracelsus first actively advocated the idea during the Renaissance, but with the flight of time it seemed to recede always farther from realization. By the 20th century scientists had concluded that human tissues were far more susceptible to the poisonous effects of disinfectants than were bacteria; hence, internal chemical

sterilization was regarded as a will-o'-the-wisp and hopes were centered on the apparently more reasonable approach of specific sera and vaccines.

By the turn of the century, the necessary ingredients were at hand for the creation of synthetic drug therapy in infectious disease. Bernard had elaborated the principles of logic for experimental attack on the problem, while development of the synthetic dye industry made possible new approaches through organic chemistry. The last element required, a pertinacious faith in the attainability of a supposedly chimerical goal, was provided by a saturnine and obstinate pathologist, Paul Ehrlich. Once something caught his interest nothing moved him. He early became obsessed with techniques for staining pathological specimens. Neither impending academic failure nor the carping of his residency chief could turn "the little dye dabbler" from the laboratory. From his innumerable experiments he learned that different dyes had specific affinity for certain cells, living as well as dead. Somewhat later, while working with Koch, Ehrlich concluded that microbes injure only those cells for which they have a chemical affinity, and then developed his theories of induced immunity. From these discoveries he was convinced that chemotherapy was entirely practicable. He set out "by dint of continuous and persistent effort applied to numerous chemical variations to discover chemicals which inflict the greatest possible injury upon the parasite without at the same time injuring the organism they infect."

The causative organism for the dread African sleeping sickness had just been isolated and scientists at the Institut Pasteur in Paris had discovered how to produce the disease in mice. Ehrlich chose this for his studies, set up an infected mouse colony and began to investigate the effect of aniline dyes on the invading microorganisms. Systematically he altered the affinity and toxicity of the dyes by subtly modifying the chemical structures of those which showed even traces of therapeutic activity. First a red and then a blue dye promised success as they, almost miraculously, cured mice of one variety of the disease. But then, at the brink of apparent victory, there were revealed a number of discouraging complexities. While Trypan red and Trypan blue were repeatedly successful in mice, in rats, guinea pigs and dogs they were hopelessly inadequate. The enigma of internal disinfection was much more complex than had been supposed. Not only the relative sensitivity

of host and parasite but the variations in susceptibility of the subvarieties of microorganisms, and species differences in the host, were all interconnected with the complexity of a Chinese puzzle. It was a sobering disillusionment, enough to blunt the ardor of the staunchest; but, possessed with a doggedness that was sometimes mistaken for stupidity, Ehrlich regrouped his personal and intellectual resources, preparing to plod ahead on a new course.

He never returned to this problem, however, because identification of the parasite which caused syphilis was announced. Its similarity to the organism of sleeping sickness, plus the terror inspired by this widespread disease, was a challenge Ehrlich could not resist. So, he turned to study syphilis, armed with the knowledge that Paracelsus had said arsenic was of value against it, and that the English had discovered an organic arsenical, which, though toxic, was useful in sleeping sickness. First, a very similar parasitic infection was produced in rats and mice; then the organic arsenic molecule was altered step by step. Finally, the 606th variation was successful. After months of careful study in animals, the first dozen patients received Salvarsan. Early doses were overgenerous and some sufferers died but the others were cured. While far from the perfectly harmless compound sought, Salvarsan was effective and stood as unassailable proof of the feasibility of systemic chemical treatment for infectious disease.

Meanwhile, a seemingly unimportant event to the U.S. pharmaceutical industry took place at Greenbush (now Rensselaer), New York. In 1903 the German firm, Bayer, bought out the Hudson River Aniline & Color Company and, while dye manufacture continued, began the manufacture of aspirin and phenacetin from imported intermediates. Henceforth, from this plant there was a steady flow of new key chemical drugs such as Novocain, the Salvarsans, Veronal, Luminal, Pyramidon, Salyrgan, etc., to all parts of the country.

Not until the turmoil of World War I disrupted receipt of all imported intermediates or finished bulk chemicals did the nation or the industry realize the inadequacy of its technical "know-how" to produce such goods from domestically available raw materials. Tragedies such as the plight of epileptics who had known freedom from their affliction while using German Luminal jarred the scientific community to frenzied efforts. In universities young chemical talent struggled with synthetic problems like the search for a feasible method of preparation for pheno-

barbital, which was carried out at the University of Chicago. Industry too was called upon by the government. Abbott Laboratories succeeded in overcoming the desperate need of the Army for procaine and barbital. From these determined efforts came the "home-grown" talent and industrial skill to produce the synthetics which had so quickly become an indispensable part of the medical armamentarium. The nation learned a bitter lesson which stimulated the development of a vigorous and expanding chemical and pharmaceutical industry.

Ehrlich had sought a more perfect fulfillment of his chemotherapeutic dream during the remaining years of his life, but his sudden death and the convulsions of World War I completely disrupted this research. When peace was restored, those in Europe who followed Ehrlich found themselves groping in his footsteps along a not yet fully understood experimental path. Thus, they deserted Bernard's principles and were doomed, like the pre-19th century biologists, to only meager success. A quarter century of labor yielded only partially successful medicaments for syphilis, a few rather indifferent anti-malarials and some imperfect drugs for African sleeping sickness—therapy which was not startlingly successful. These were protozoan diseases caused by complex parasites of the animal kingdom which were not the major destroyers of mankind. It was bacterial diseases which slashed gaping holes in the ranks of the living. Much smaller single-cell plant-like organisms caused the tuberculosis, pneumonia, peritonitis, septicemia, meningitis and puerperal fever that were dreaded by both physician and patient. Bewildered by the lack of success against this type of disease, men's enthusiasm for chemotherapy ebbed and in despair Salvarsan was sometimes branded a fluke, and Ehrlich an unsound visionary whose basic tenets led nowhere. So, one by one they turned away from chemotherapy to sera, vaccines and tissue extracts.

What was wrong? Many of these infections could have been duplicated in test animals so that experimental study was possible, yet no great progress was forthcoming. At that time most of the successful synthetic anti-infective drugs contained elements like arsenic which were known to be poisonous. But this only seemed to confirm Ehrlich's idea of specific microbe poisons innocuous to the host. Mistakenly, many of his successors approached the problem cart-end first by starting with toxic elements like arsenic, bismuth and mercury and trying to find forms in which these would be better tolerated by man than by

microbe. They become so enamored of toxic elements that they lost sight of Ehrlich's earlier success with dyes and his alternate suggestion that interfering with bacterial metabolism might offer another path of attack. How simple it now seems. Plants are nourished in a manner different from man, and so it would appear logical to find a chemical innocuous to humans which would give microbes such "indigestion" they would starve to death. But instead of searching for new ideas, facts were fitted to the specific poison theory and it was actually held during the 1920's that bacteria, in contrast to the complex protozoa, as a primitive form of life were so adaptable to adverse environment that they could resist any toxic compound which human tissues could tolerate. Here was a paradox: the only hypothesis demonstrated to work was pronounced unworkable.

Progress on the industrial side, however, was phenomenal. At the outbreak of World War I American pharmaceutical producers were quite incapable of turning out the few synthetic drugs then in use. As late as 1917 the domestic dye industry was largely lacking in the equipment needed for organic syntheses on a commercial scale and metallurgists and equipment makers in this country had little experience in turning out the more complex apparatus which up till then had been entirely imported. Even so, full scale manufacture was out of the question without an adequate supply of basic chemicals from by-product coking and petroleum cracking. A good flow was not achieved until after hostilities had ceased and European supplies were once more available. Fortunately, this did not deter the synthetic industry for, having learned a bitter lesson from their inadequacies, they carried through wartime plans and trained personnel, expanded, and equipped plants fully capable of turning out the chemicals and synthetic drugs we now know were vital.

At this time most of the impetus in medicinal chemical research remained in Europe, and somehow, through all this era of doubt, the German chemical industry clung to the possibility of utilizing dyestuffs. Thus, about 1930 a young scientist, Gerhard Domagk, was given the assignment of finding a synthetic remedy for infections. Day after day Domagk turned his infected mice to every shade in the spectrum as he went through the dye samples which seemed to flow unendingly from the chemical storeroom shelves. Here and there, he noted a hint of activity; and then every conceivable chemical relative of the promising

dye was tested from his shelves or synthesized in the chemistry laboratories. After more than two years of tedious elimination Domagk found a brilliant red dye which saved infected mice from certain death. Not long after, a bottle of dusky red tablets was sent to a clinic for trial in human infections. The first case was a little 10-month old baby dying from an overwhelming skin infection of staphylococci which had invaded the bloodstream. Three days later the baby was startlingly carmine-hued from the dye, but the infection was gone. Immediately thereafter, the drug was tried successfully in pneumonia, meningitis and a long list of other serious infections. Then, in 1935, these ruddy little tablets were dubbed "Prontosil" and announced to the world. Within a year chemists at the Institut Pasteur in Paris discovered that the active principle of this chemically complex dye was a simple, colorless well-known dyestuff intermediate now called sulfanilamide.

In spite of the excellent results reported in Europe, the long years of little progress after Ehrlich had ingrained a deep disbelief about the validity of any report of successful chemotherapy. In the United States, as in Great Britain, exhaustive confirmatory animal tests were followed by cautious and skeptical human trial. Then the dramatic cure of the President's son from a seemingly fatal infection made the sulfa drugs front-page news.

At last, chemists and biologists had found a guide-post in the wilderness that had been chemotherapy. From laboratories all over the United States, such as Merck, Sharp & Dohme, Lederle, Winthrop, Monsanto, and Squibb, and from Europe as well, innumerable "sulfas" came tumbling out to attack "strep" and "staph" infections – and pneumonia, meningitis, gonorrhea, mastoiditis, and peritonitis too. They did not poison with toxic elements like arsenic but quite literally starved the bacteria to death by interfering with their nutrition. Death from dozens of once fatal diseases became less common and man's life span spurted upward.

With the discovery of sulfa drugs and antibiotics and new biologicals, death rates from infection have tumbled almost to the vanishing point. Tuberculosis, once the "captain of death", killed 500 per 100,000 population in 1850. Now, largely due to a method of producing experimental tuberculosis in animals which permitted search for chemotherapeutic weapons against it, the United States mortality in 1955 was about 10 per 100,000 and the rate is dropping steadily each year. Similarly, in the

20 years between 1933 and 1953, surgical appendicitis deaths were reduced to one-tenth of the pre-sulfa numbers as a direct consequence of the use of drugs developed through experimental studies of infections.

Malaria, once a racking lifetime ague, now not only can be controlled but cured in a few days by synthetic drugs, some like atabrine and Aralen originally from Europe, others like Plaquenil, Camoquine and Primaquine from the wartime cooperative program, or continuing efforts such as those at Parke Davis and the Sterling-Winthrop Research Institute. The conquest of each disease has come as the result of our ability to reproduce the infection in experimental animals and, therefore, to study the action of chemicals on it under controlled conditions according to Bernard's and Koch's precepts.

In the last quarter century improved synthetic drugs for the cure of infection, palliation of symptoms, and surer x-ray or laboratory diagnosis have come pouring out from the American pharmaceutical industry. With the advent of World War II, and the tremendous therapeutic advances sparked by our industrial research, the flow of new drugs from Europe to our nation has largely reversed, and now the world looks to us for the new synthetic remedies that will preserve life and, increasingly, make it worth living.

This has been accompanied by a tremendous expansion in the volume of use of pharmaceuticals. In 1939 the total drug sales, at manufacturers' price levels, was 301 million dollars. Eighteen years later in 1957 it had jumped to 2102 million dollars, a seven-fold increase. During this period, sales of the proprietary drugs advertised directly to the lay public went from 152 million to 425 million dollars, an increase of 2.8 times. But in contrast, the drugs used solely by physicians, the so-called ethical drugs, jumped from 149 million to 1677 million dollars, an increase of 11.3 times. It can be seen that the great increase has been in the potent specific drugs which require professional supervision to use.

Such volume of production could not have been achieved without tremendous expansion of the pharmaceutical industry. All through the 1930's a multitude of automatically controlled synthetic operations were introduced. New or improved control instruments kept untiring watch on the innumerable conditions which governed the synthesis of increasingly complex chemical drugs. From better temperature gauges to photoelectric eyes, electronic controls and spectrographic analysis, every device to improve quality has been utilized. The newest high strength

corrosion resistant alloys permit much larger and more efficient equipment, especially for reactions carried out at high pressures. This has been accompanied by a steadily increasing quality of production, and a continuously decreasing cost of the drugs. Today the drugs required to cure an illness cost less than ever before, even though hospital costs and other ancillary expenses seem to have skyrocketed. Thus, the national average total expenditure for drugs in 1957 was only about $12.00 per person, while three times this amount was spent on tobacco and over four times as much on alcoholic beverages.

But the greatest saving in costs of medical care has not been in the price of the medicine, but in the reduction of duration of illness and losses through sickness and death. As our new chemical bullets become more potent and specific they are virtually eliminating one after another of the hitherto important causes of disability and death. The pharmaceutical industry can take justifiable pride in its share of this contribution to national welfare.

Projection of the present rates of increase in life span indicates that we may look forward to an average length of life of about 100 years by the end of this century. However, there will be no zest in life at 100 or 150 years of age if the mind is misty, eyes and ears untrue, the bones too brittle and one's digestion awry. As we subdue each former source of disability, control of the remaining diseases becomes more urgent. Thus, a whole new division of medicine, geriatrics, is being created to deal with the special problems of the aged. The development of worn-out organs and flagging minds must be prevented by new therapeutic discoveries. Too new to have made many major advances, geriatric medicine is attracting increased and vigorous attention in the American pharmaceutical industry, and will play an ever-widening role as we move toward the 21st century.

In retrospect, the whole process which is making life so much longer and more livable began a century ago when chemists, like Liebig, began to probe the potentialities of organic chemistry and Claude Bernard developed the concepts and methods essential to the systematic application of experimental reasoning to biological research. Through these techniques Pasteur, Koch and Ehrlich set in motion unparalleled progress in medicine and therapeutics by use of both the methods and fruits of chemical synthesis. Yet all of this would have been of but limited effect had not the simultaneous development of

a responsible, competent pharmaceutical industry made available these new synthetic medicines in large quantity, high quality, and at steadily decreasing cost to vast segments of the world's population. Only the extensive experience and mass production of techniques of the pharmaceutical companies could have brought these wonder-working chemical bullets within the present reach of every man.

A highly skilled synthetic pharmaceutical industry has replaced the drug store back room of a century ago as the helpmate of the physician in the endless struggle against suffering and death. Through the years this industry has grown not only in ability and facilities but in responsibility to mankind through the profession it serves. Hundreds of thousands of men and women in its employ are devoted to the search for new and better ways to meet the challenge of present medical problems. There is every promise of continuing success. With each will come profound changes and new problems to be met in the spirit of Paracelsus, of Claude Bernard and of Paul Ehrlich.

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*Brown, S. S.; Libo, H. W., and Nussbaum, A. H.: Norethandrolone In the Successful Management of Anorexia and "Weight Lag" in Children, Scientific Exhibit presented at the Annual Meeting of the American Academy of Pediatrics, Chicago, Oct. 20-23, 1958.

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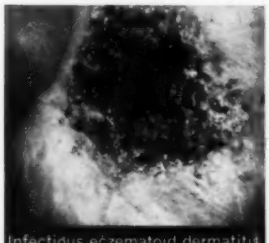

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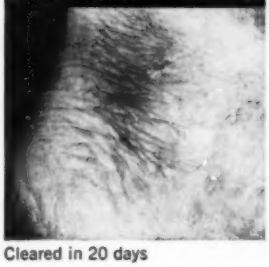

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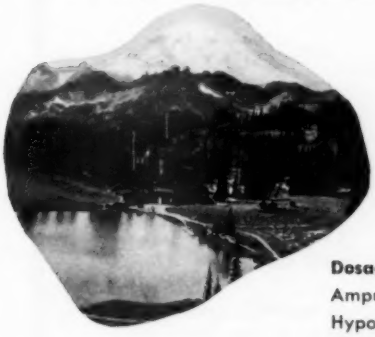

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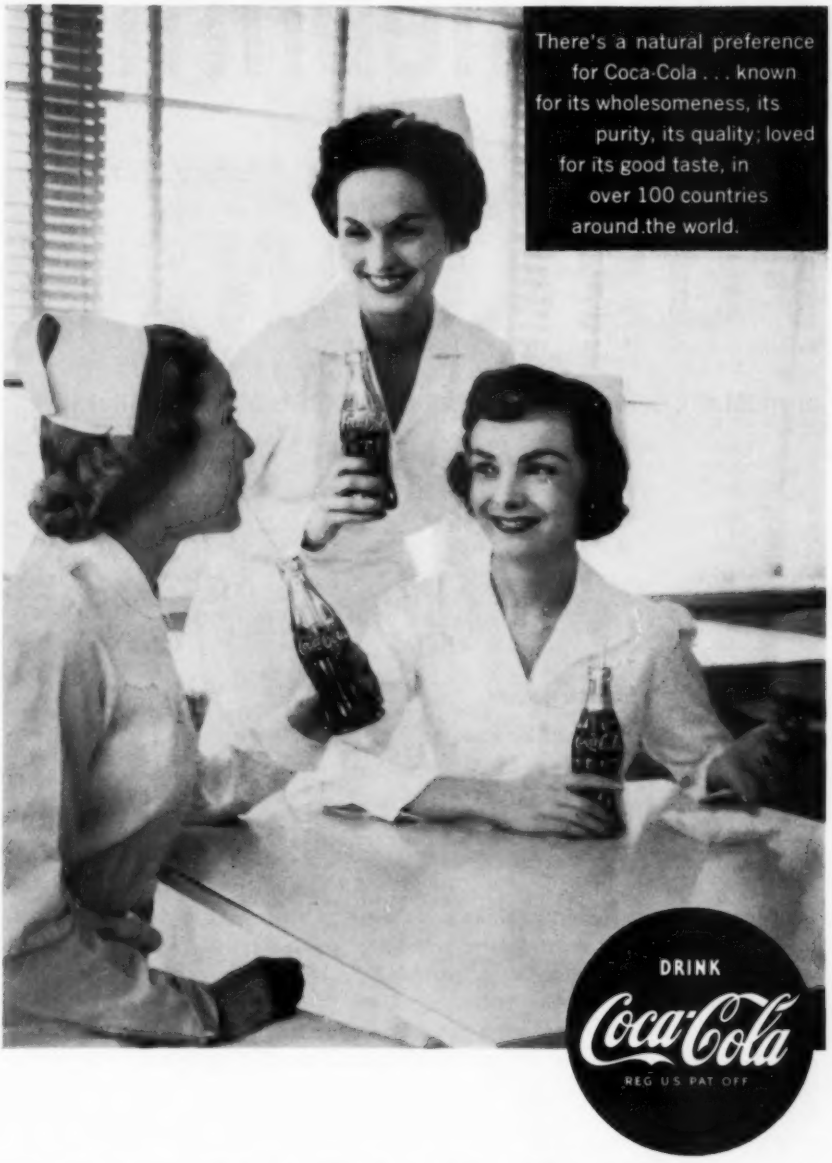

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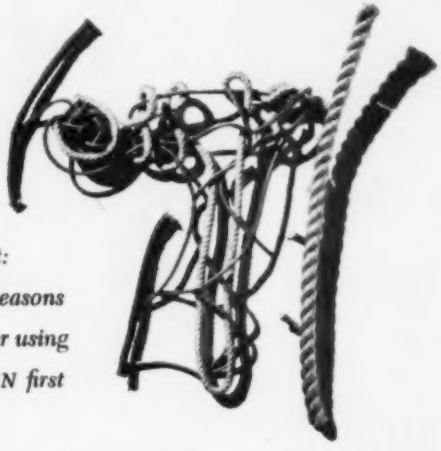

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